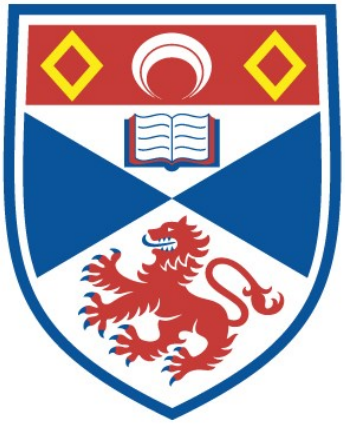
SYNTHESIS OF THE ORIGINALLY PROPOSED STRUCTURE OF PALMEROLIDE C

Joanna Wlochal

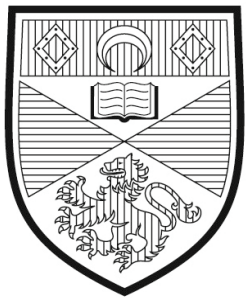
A Thesis Submitted for the Degree of PhD
at the
University of St Andrews



2012

Synthesis of the Originally Proposed Structure of Palmerolide C

Joanna Wlochal
School of Chemistry



University of St Andrews

600 YEARS

June 2012

Thesis submitted to the University of St Andrews for the degree of Doctor of Philosophy

Supervisor: Dr. Gordon J. Florence

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I, Joanna Wlochal, hereby certify that this thesis, which is approximately 45000 words in length, has been written by me, that it is the record of work carried out by me and that it has not been submitted in any previous application for a higher degree.

I was admitted as a research student in May, 2008 and as a candidate for the degree of PhD in April 2012; the higher study for which this is a record was carried out in the University of St Andrews between 2008 and 2012

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“Believe that you can do it, under any circumstances”

- Maria Skłodowska-Curie

Dedicated to my mother and father

Preface

This thesis describes the work carried out during my three and a half years as a Ph.D. student at the School of Chemistry, University of St Andrews under the supervision of Dr. Gordon J. Florence. There are numerous people that have contributed and been involved in the projects I have worked on in the last few years and I would like to thank the following people for their help and collaboration.

I am deeply grateful to Dr. Gordon J. Florence for giving me the confidence to explore my research interests and the guidance to avoid getting lost in my exploration through sharing with me his vast knowledge of chemistry. Gordon was a fabulous advisor: sharp, cheery, perceptive, and mindful of the things that truly matter. He has always motivated and inspired me and during the hard times, remained optimistic and led me in the right direction. Thanks for believing in me.

I would also like to thank my assessor Prof. David O'Hagan for continuous interest in my progress, encouragement and support. I owe many thanks to Dr. Andrew Smith for providing me with scientific insight on numerous occasions, particularly during joint group meeting sessions. Dr. Iain Smellie also deserves a special thanks; he was always full of sound advice when proof-reading this thesis, and was always able to foster a great learning environment for undergraduate students during the time I assisted in his lab-courses.

During my graduate studies I have had the privilege of working with a number of interesting and exceptional people and I would like to take the opportunity to thank them individually. When I first came to the BMS 4th floor, the older students and staff at the School of Chemistry helped to shape me as a scientist. In particularly Dr. Ross G. Murray provided a great deal of guidance during the early years; his work ethic, expertise and music taste kept me coming back every morning, believing my chemistry would start working… and it eventually did! Agnieszka Kosinska took great care of me in and out of the lab, ever since I came for an interview and then through out the first year. I would like to collectively thank the GJF group for making our laboratory a great working environment. There are also a number of people whom I would like to acknowledge individually: the witches from Florence/Florence witches as you like (yes that's about you

Jo and Katy) thanks for all the sabbatical sessions helping to keep in balance with work, all the support, encouragement, and friendship. Katy deserves all the credit for any coherence in the following pages; Jo, I bet… she would have proof-read your thesis too, if she wouldn't be finishing sooner. The later group members, especially Greg for sharing my 'joy' when I saw the spectra for my final product; to both you and Lloyd, thanks for being understanding lab- and office-mates. Dr. Lik Ren Tai thanks for possibly the most easy going post-doc attitude I have ever come across. I had the good fortune to work with one outstanding undergraduate; Euan, despite sharing my fume-hood and not working on my project, you were by far the best and most cheerful student I have worked with. Guys, having supportive bay mates, and walking this rocky way with me, made a significant difference in my postgraduate experience.

The list of people I would like to thank goes on and on. The Botting, O'Hagan and Smith labs have all been extremely helpful in sharing their lab resources and knowledge. Thank God I had Su one step ahead of me, reminding of any upcoming deadlines for reports and PG bureaucracy to be dealt with; Nikos, for cheering me up when it was needed. I have many fond memories, especially from time spent with Jason, thanks mate. Thanks also to the Polish crew, whom I was fortunate to meet in St Andrews especially Ola, Lila, Artur, Piotr, Ilonka, Gosia and Kris; not a single one of them has ever refused to lend a hand my way. I would also like to thank my friend far away from Scotland, Alma, studies at Lund was the first period in my life where I was living away from my entire family. Fortunately, I met you and you made me feel at home. Your friendship is one of a kind, forgive my negligence over the past years. Thanks for helping me get through the difficult times, and for all the emotional support, camaraderie, entertainment, and care you provided.

For facilities, I would like to thank Dr Tomas Lebl and Melanja Smith in the NMR lab. Caroline Horsburgh and the National Mass Spectrometry Centre in Swansea for mass spectrometry analyses. This project would not be realised without the generous financial support of the University of St Andrews and the EPSRC research council.

At this point, I would like to thank the most important people in my life, my family. I am nothing without them. As much as my time at St Andrews has shaped me as a scientist over the past three-plus years, the continuous support of my parents and sisters

have helped define me over more than a quarter of a century. My mother, Danuta, is the backbone of our family. She has sacrificed everything to ensure that my sisters and I would always be able to strive for our goals. If there would be a Ph.D. in life in general she would definitely earn *summa cum laude*. My father, Adam, who I want to thank for showing me the big world, for telling me that nothing is impossible, just further away to reach. He has also taught me the value of hard work. My older sister, Marlena-Zocha, as the eldest paved the way, making my life easier on many occasions, thanks for keeping me up-to-date with everything else beside chemistry, I wish you all the joy and happiness, and remember you are always welcome wherever I go. My younger sister, Alicja, for always bringing good news, tak for al jeres støtte og opmuntring, hvad der går rundt kommer tilbage omkring ;-)

Finally, I want to thank Josep for never giving up on me. It happened to be a distant journey for both of us, the journey that I learnt to cherish, more than a destination…

What else could I write? I don't have the right

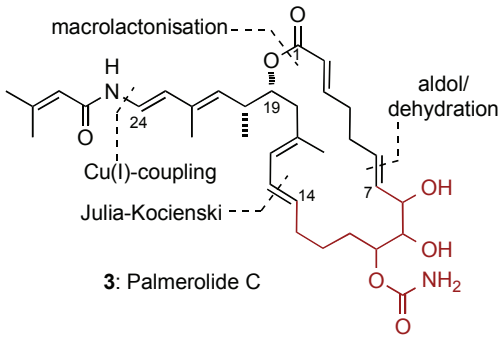
Joanna Wlochal

St Andrews, 15th June 2012

Abstract

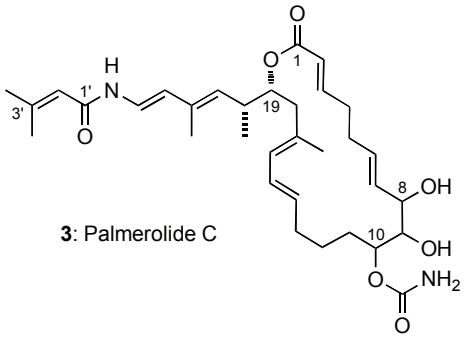
The palmerolides are an emerging class of polyketide natural products isolated from marine organisms inhabiting the Antarctic Sea. Although there has been a substantial effort to prepare the most active family member palmerolide A, no synthetic work has been performed in the area of the other members of the family; palmerolides B and C of different ring structure. These compounds are particularly interesting due to their complex structures with undefined stereochemistry and both display high selectivity towards human melanoma cancer cell lines.

A highly convergent strategy to access palmerolide C has been developed, relying on the assembly of three fragments using key bond couplings at C6-C7 (boron-mediated aldol reaction/dehydration) and C14-C15 (Julia-Kocienski olefination), followed by a suitable macrolactonisation step and Buchwald enamide formation. Prior to subunit synthesis, the relative configuration of the C8-C10 stereotriad was resolved *via* the synthesis of diastereomeric degradation fragments by the application of organocatalytic cross aldol reactions and a suitable 1,3-selective reduction.



Compound Numbering

All compounds intended toward the structure elucidation or total synthesis of palmerolide C will be numbered according to the carbon chain of the natural product. This numbering is given on the structure and is used in the ^{1}H NMR assignment.



3: Palmerolide C

The naming of the compounds in the experimental section uses the IUPAC convention.

List of Abbreviations

aq	aqueous
ASAP MS	atmospheric solids probe analysis mass spectrometry
[α]	specific rotation
Ac	acetyl
AcOH	acetic acid
Ar	argon
ATPH	Aluminium tris-(2,6-diphenyl)-phenoxide
BT	benzothiazol-2-yl
br	broad (NMR)
Burgess reagent	methyl N-(triethylammoniumsulfonyl)carbamate
calcd	calculated
d	doublet
c	concentration
CD	circular dichroism
CM	cross-metathesis
COSY	correlation spectroscopy
d	doublet
d_6-DMSO	deuterated dimethyl sulfoxide
DBU	1,8-diazabicycloundec-7-ene
DCC	dicyclohexylcarbodiimide
dd	doublet of doublets
de	diastereomeric excess
decomp.	decomposition
DIAD	diisopropyl azodicarboxylate
DIBAL-H	Diisobutylaluminium hydride
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin Periodinane
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio

δ	nuclear magnetic resonance chemical shift [ppm]
ee	enantiomeric excess
EI	electron ionisation
eq	equivalent
ES	electrospray
Et	ethyl
EtOAc	ethyl acetate
g	gram(s)
h	hour(s)
HMBC	heteronuclear multiple-bond correlation spectroscopy
HMPA	hexamethylphosphoramide
HRMS	high-resolution mass spectrometry
HSQC	heteronuclear single-quantum correlation spectroscopy
HWE	Horner-Wodsworth-Emmons reaction
Hz	Hertz
IC_{50}	concentration required for 50% inhibition (of biological effect)
Im	imidazole
IR	infrared
J	coupling constant
L	litre
LDA	lithium diisopropylamide
L-Selectride	lithium tri-*sec*-butylborohydride
m	multiplet (NMR)
M	molarity
Martin sulfurane	bis[α,α-bis(trifluoromethyl)benzenemethanolato]diphenylsulfur
m/z	mass to charge ratio
Me	methyl
MeOH	methanol
MHz	megahertz
min	minutes
mol	mole
MOM	methoxymethyl ether
MS	mass spectroscopy

MTPAA	α-methoxy-α-(trifluoromethyl)phenyl acetic acid
MW	microwave
μ	micro
NaHMDS	sodium hexamethyldisilazide
NMP	*N*-methylpyrrolidone
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
Nu	nucleophile
°C	degrees Celsius
Obs	obscured
p	para
pH	-log[H+]
Ph	phenyl
PMB	para-methoxybenzyl
ppm	parts per million
PT	phenyl tetrazole
py	pyridine
q	quartet (NMR)
rt	room temperature
Rf	thin-layer chromatography retention factor
s	singlet (NMR)
t	triplet (NMR)
t	tertiary (*tert*)
TBAF	tetrabutylammonium fluoride
TBS	*t*-butyldimethylsilyl
TEA	triethylamine
TEMPO	2,2,6,6-tetramethyl-piperidin-1-oxyl
TES	triethylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl

Contents

Chapter 1

1.1 Discovery of the palmerolides

The Antarctic polar region is one of the least explored places on our planet due to its inaccessibility. Nevertheless, what is known about its fauna and flora has significantly contributed to our general knowledge of life and uncovered amazing examples of evolutionary adaptation for survival in extreme environmental conditions.[1] Importantly, this ecosystem has remained undisturbed for millions of years. As a result, the unique phylogenesis of the marine fauna of the Antarctic seas offers distinct structural and functional properties in the secondary metabolites produced by the indigenous species.[2]

In 2006 Baker and co-workers reported the discovery of a family of marine macrolides, which were isolated from the tunicate *Synoicum adareanum* (Figure 1.1.1) inhabiting the shallow waters in the vicinity of Palmer Station, the only US station on Antarctica north of the Polar Circle.[3] The isolated compounds were named the palmerolides in recognition of Palmer Station, where they were found. This particular tunicate, found in abundance on the benthos of the Antarctic Sea grows from a common base to multiple fist-sized groups of colonies providing sufficient biomass for collection without harm to the ecosystem. The fact that even a single colony could deliver hundreds of milligrams of palmerolides after processing limited the harvest to a minimum. However, the yields of isolates were variable between colonies, as was the distribution of over a dozen different palmerolides identified.[4] With the discovery of the palmerolides, Baker has drawn more attention to the potential of Antarctica's remote and unexplored resources.

Figure 1.1.1 *Synoicum adarenum* collected at Palmer Station, Antarctica (Photograph supplied by Bill J. Baker, University of South Florida, USA)

1.2 Isolation and structure determination

The collected material was phytochemically processed by first freeze-drying the harvested tunicates to provide 520 g of dry biomass. The initial extraction with dichloromethane and methanol took three days and resulted in a reddish-brown semi-solid upon evaporation. The crude extracts were then partitioned between ethyl acetate and water. The organic layer was washed, dried and evaporated to provide material for flash column chromatography. The initial isolation gave several separate fractions, which were then purified by reversed-phase HPLC to deliver pure compounds for analysis.

Assessment of the biological activity of the palmerolides began with a 60-cell line panel screen at the National Cancer Institute which revealed unique biological profiles in targeting human cancers. Selectivities towards UACC-62 and M14 melanoma cancer were determined with IC_{50} of 18 and 76 nM for palmerolide A (**1**), rendering the isolated compounds potential candidates for future drug development. In this light the structures of isolated natural products had to be determined.

Investigation of the structural composition of palmerolides by Baker and co-workers culminated in detailed elucidation of the planar structure of twelve family members along with the proposed configurational assignment of palmerolide A (**1**). The structural characteristics were determined by NMR spectroscopic and HRMS spectrometric experiments.[4]

Structurally, the isolated compounds comprise a 20-membered macrolactone ring bearing a carbamate group at one of the oxygenated positions and four *E*-configured double bonds including an *(E,E)*-diene motif at C14 within the macrolide. In addition, a single side chain of varied length and functionality has been identified attached to the C19

carbon. The palmerolides were then grouped according to the macrolide core structure (Figure 1.2.1). The three different ring systems were distinguished by the structural variation spanning the C6-C11 region of the macrolactone with altering hydroxylation/unsaturation patterns. All the elucidated compounds within these groups bear one of the five different side chains and will be presented in the following sections (1.2.1-1.2.3). It was found that the first compounds isolated, named palmerolide A (**1**), B (**2**) and C (**3**) each represented one of the three unique ring systems (Figure 1.2.1).[4]

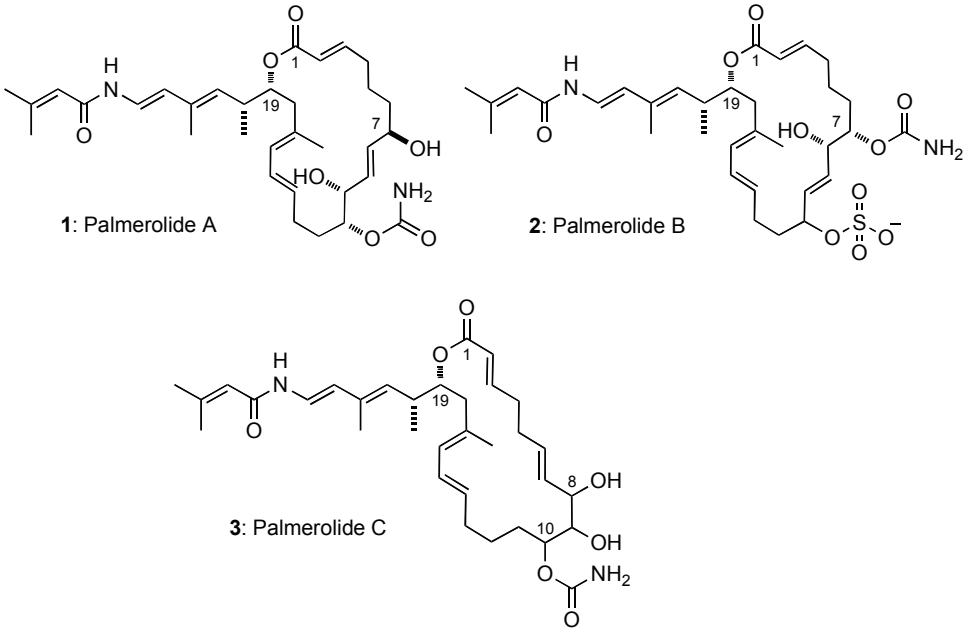
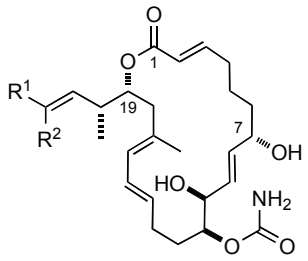


Figure 1.2.1 Three unique ring systems found in the palmerolide family with preliminary stereochemical assignment.

1.2.1 A - ring system

Palmerolide A was found to be the primary isolate both in quantity (200 mg, 0.02% dry wt.) and biological activity (melanoma UACC-62, IC_{50} = 18 nM). As a result it has received the majority of the attention from the synthetic organic community.[5-8] The first total synthesis of palmerolide A, achieved by De Brabander within a year from the isolation report, reassigned the proposed relative configuration of **1** and established the absolute stereochemistry to be as shown in **4** in Table 1.2.1. Elucidation of the planar structure by Baker and co-workers revealed a distinct macrolide with a hydroxyl at C7 separated by a di-substituted olefin from the dihydroxyl motif at C10 and C11. The relative configuration of palmerolide A (**1**) was established by chemical derivatisation with chiral reagents (MTPA esters of C7, C10 hydroxyl-bearing stereocentres analysed using the

Mosher method, as discussed further in section 2.2.1) and NMR experiments (*J*-based configurational analysis of C11 using the Murata method).[3] While the Murata analysis[9] was conducted correctly, it was realised after the first synthesis of **1** by De Brabander that the Mosher ester derivatives were incorrectly assigned. The incorrect interpretation of the C7 and C10 configuration arose as a direct consequence of the applied derivatisation method with (*R*)-MTPA acid chloride, where change in priority of substituents relative to (*R*)-MTPA acid went unnoticed and resulted in the formation of the (*S*)-MTPA ester, not as assigned (*R*)-MTPA ester.[3]



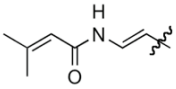
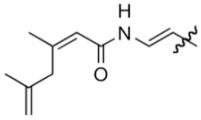
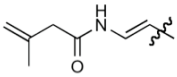
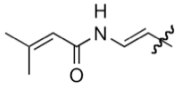
Entry	Compound	R^1	R^2
1	Palmerolide A (**4**)		$-CH_3$
2	Palmerolide D (**5**)		$-CH_3$
3	Palmerolide E (**6**)	CHO	$-CH_3$
4	Palmerolide F (**7**)		$-CH_3$
5	Palmerolide G (**8**)	$-CH_3$	

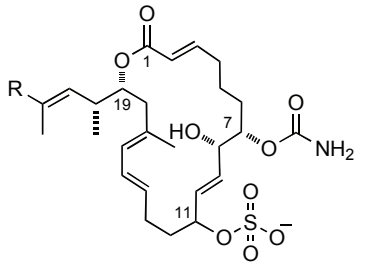
Table 1.2.1 The palmerolides with ring system A with corrected stereochemical assignment.

Structural analogues of palmerolide A (**4**) have been identified based on the comparison of the collected NMR data. Four palmerolides were found to have the same ring type but varied in the composition of the side chain (Table 1.2.1). The primary isolate (**4**) comprised of conjugated enamide. Further palmerolides of this ring type presented isomerisation, extension or disruption in conjugation in their side chains (Table 1.2.1).[10] Palmerolide D (**5**) was found to contain an elongated side chain with one (*Z*)- and one terminal double bond, in contrast palmerolide E (**6**) bears a side chain truncated by one carbon at C-23 terminating in an aldehyde. Shift from conjugation in the enamide to a

terminal double bond was identified in palmerolide F (**7**) and the isomeric (*Z*)-geometry of the C21/C22 olefin distinguished palmerolide G (**8**).

1.2.2 B - ring system

A distinctive pattern of hydroxyls at C7 and C8 separated by an olefin from the C11 hydroxyl constitute the B-ring macrolide system. The presence of a sulfate group, not found in the other palmerolides substantially affects the properties of the compounds with this core structure, making them very polar and prone to hydrolysis (Table 1.2.2). Determination of the planar structure of palmerolides B (**2**) and H (**9**) by NMR spectroscopy proved difficult due to their instability in dimethylsulfoxide. Although, the first attempt to obtain spectroscopic data for **2** and **9** ended with decomposition of the isolates, further NMR experiments carried out in methanol allowed their structure elucidation. It was found that the side chains of palmerolides B (**2**) and H (**9**) correspond to the previously described structural motifs found in palmerolide A (**4**) and D (**5**).



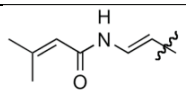
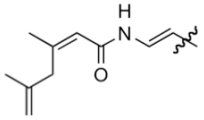
Entry		R
1	Palmerolide B (**2**)	
2	Palmerolide H (**9**)	

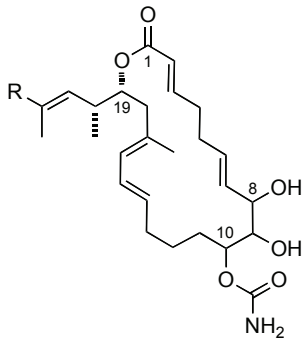
Table 1.2.2 The palmerolides with ring system B with preliminary stereochemical assignments.

Determination of the relative stereochemistry of the C7-C11 stereocentres proved challenging. Chemical derivatisation resulted in the elimination of the sulfate group and hydrolysis of the carbamate. Nevertheless, the C8-Mosher esters were formed and the absolute configuration of the C8 hydroxyl was established. Advanced spectroscopic experiments (gHSQMBC) provided information on the homo- and hetero-nuclear *J*-coupling constants and allowed the determination of the *syn* arrangement of the C7-C8

stereocentres. Unfortunately, based on the available data, the configuration of the isolated C11 stereocentre could not be deduced.[10]

1.2.3 C - ring system

The final two palmerolides representing the C-ring system, were identified as regioisomers of palmerolide A (**4**) and E (**6**). A motif of three contiguous stereocentres at C8-C10 distinguishes palmerolide C (**3**) and K (**10**) (Table 1.2.3) from the other family members. Spectroscopic parameters for the C19-C20 positions were found to closely match data reported for the analogous centres in palmerolide A (**4**). Consistent with a common biogenesis and supported by NMR comparison, the C19-C20 stereogenic centres were determined to have the same configuration within the entire family.[11] The side chain identified in palmerolide C (**3**) corresponds to the (*E,E*)-1,3-dienamide found in palmerolide A (**4**). Palmerolide K (**10**) is truncated at C23 with an aldehyde similar to palmerolide E (**6**). The assignment of the relative and absolute stereochemistry of the remaining centres was not available until recently.[4] The stereochemical assignment of the C8-C10 stereotriad became one of our major objectives and will be discussed further in Chapter 2.



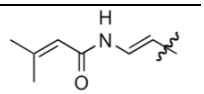
Entry		R
1	Palmerolide C (**3**)	
2	Palmerolide K (**10**)	CHO

Table 1.2.3 The palmerolides with ring system C.

Characteristic structural features of palmerolides, namely carbamate and enamide side chain suggest involvement of, as yet unknown, bacterial organism in production of

these natural products in host tunicates. It has been hypothesised that a biosynthesis occurs by hybrid polyketide synthase (PKS)/nonribosomal peptide synthetase (NRPS) pathway.[12] The macrocyclic part of the molecule could be composed by modular Type I polyketide synthase operative *e.g.* in the biosynthesis of epothilones (Figure 1.2.2).[13] Formation of the side chain present in palmerolides may be initiated by NRPS-catalysed incorporation of an amino acid such as glycine (Gly)[14] and/or valinylglycine (Val-Gly).[15] Amide portion of the side chain could originate from acetate via an HMG-CoA (3-hydroxy-3-methylglutaryl-CoA) synthase-type methyltransferase.[16,17]

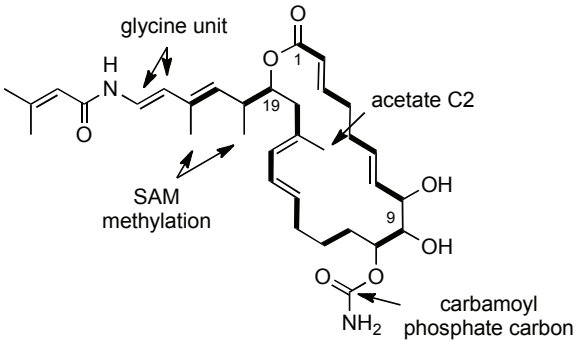
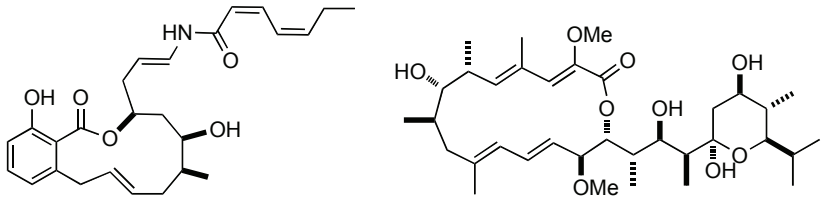


Figure 1.2.2 Hypothesised biosynthetic origin of palmerolide C.

1.3 Biological activity and SAR studies

Baker reported that the toxicity profile of the palmerolides correlates with those of several known vacuolar-ATPase inhibitors (salicylhalamide A (**11**),[18,19] bafilomycin A (**12**),[20] Figure 1.3.1).[10] Therefore, it was suggested that palmerolides mode of action might be related to an already known inhibition mechanism and undertaking further biological studies would provide relevant information supporting this hypothesis.

Vacuolar-ATPases (v-ATPases) operate as pH modulators and are widely expressed in eukaryotic cells, as well as metastatic cancer cells. The regulation of the inter- and intra-organellar acidity within various mammalian cell types is required for a variety of physiological functions including membrane and organellar protein sorting, neurotransmitter uptake, cellular degradative processes, and receptor recycling.[18] Being responsible for vast molecular regulatory functions, this proton pump system is an interesting target for pharmaceutical research and development. New biological agents, such as the palmerolides, aiming at the control or inhibition of v-ATPase enzymes are of great interest and might serve as potential cancer therapeutics.



11: (-)-Salicylhalamide A **12**: Bafilomycin A

Figure 1.3.1 Inhibitors of the v-ATPase enzyme.

Studies undertaken by Baker on the molecular mode of action revealed that palmerolide A (**4**) affects genes regulating the cholesterol and fatty acid biosynthetic pathway in malignant cells. As this was consistent with published changes in gene expression for bafilomycin A (**12**), they measured the transcriptional consequences of bafilomycin treatment on the melanoma cell lines (UACC-62 and LOX), and found correlations between the 900 genes dysregulated by palmerolide A (**4**) and bafilomycin A (**12**). Bafilomycin has been reported to inhibit cholesteryl ester synthesis through sequestration of free cholesterol in the endosomal/lysosomal compartment as a consequence of v-ATPase inhibition. The high degree of coherence between their gene profiles supports the premise that palmerolide A is a v-ATPase inhibitor, and consequently has an effect on cholesterol sequestration.[10]

On the other hand, De Brabander performed studies on the *in vitro* inhibition mechanism of v-ATPase by salicylhalamide A (**11**),[19] which contains a conjugated enamide, a structural motif shared with palmerolides. This research established several important features regarding interactions of **11** with v-ATPase enzymes. Salicylchalamide A follows a distinctive mechanism of action from bafilomycin A[20] in that it does not compete with it for binding to v-ATPase. In addition, the recognition and binding site for salicylhalamide A was identified to be within the membrane embedded V_0 domain of v-ATPase enzyme. Interestingly, without the enamide side chain salicylhalamide A loses activity. Further biological assays provided evidence that **11** does not inhibit the ATP hydrolysis activity of the dissociated V_1 domain of the v-ATPase but instead affects the ATPase activity of the holoenzyme by inhibiting the V_0 domain. Salicylihalamide A causes a dramatic redistribution of cytosolic V_1 from a soluble to a membrane-associated form, a change not observed in cells treated with either bafilomycin A (**12**) or NH_4Cl.

Further studies are underway to fully establish the mode of action displayed by the palmerolides, as investigations to date provided some insight but do not answer all the questions in this aspect. In addition, the structure-activity relationship of the palmerolides clearly indicates the importance of the carboxamide side chain for biological activity (Table 1.3.1). Palmerolide A (**4**) displayed remarkable activity in both targeting v-ATPase enzyme and three orders of magnitude greater selectivity towards human melanoma cancer UACC-62 than other cancer cell lines. In contrast, palmerolide E (**6**), with a terminal aldehyde at C23, showed a significant loss in specific enzyme activity but relative cytotoxity towards melanoma cells was retained at reduced levels (Table 1.3.1). Following the structural analysis, palmerolide D (**5**) with an extended side chain and ring system A proved to be more cytotoxic in comparison to (**4**), although slightly less selective towards v-ATPase. Terminal double bond shifted from conjugation in palmerolide F (**7**), consequently reduces the cytotoxicity and diminished enzyme activity. Palmerolide B (**2**) displayed potent enzyme selectivity, but cytotoxicity was compromised. Palmerolide C (**3**) showed reduced selectivity and cytotoxicity, however remaining in the nanomolar range (Table 1.3.1). Overall, structure-activity investigation might be inconclusive as even within the same ring type selectivity and cytotoxicity significantly fluctuates.[4,21]

Compound	V-ATPase (μM)	Cytotoxicity IC_{50} (μM)
	Mammalian	UACC-62 melanoma
Palmerolide A (**4**)	0.002	0.024
Palmerolide B (**2**)	0.023	0.250
Palmerolide C (**3**)	0.150	0.062
Palmerolide D (**5**)	0.025	0.002
Palmerolide E (**6**)	>10.000	5.000
Palmerolide F (**7**)	0.063	0.758

Table 1.3.1 Bioactivity data for palmerolides.

Since its initial disclosure palmerolide A (**4**) was identified as a very potent melanoma cancer inhibitor, it received considerable synthetic attention with several total syntheses and formal approaches published to date[5-8] and selected syntheses will be presented in the following section (1.4). Palmerolide C (**3**) and palmerolide B (**2**), on the other hand, have not been investigated synthetically as their relative stereochemistry remained unknown and selective cytotoxicity was moderately reduced compared to palmerolide A.

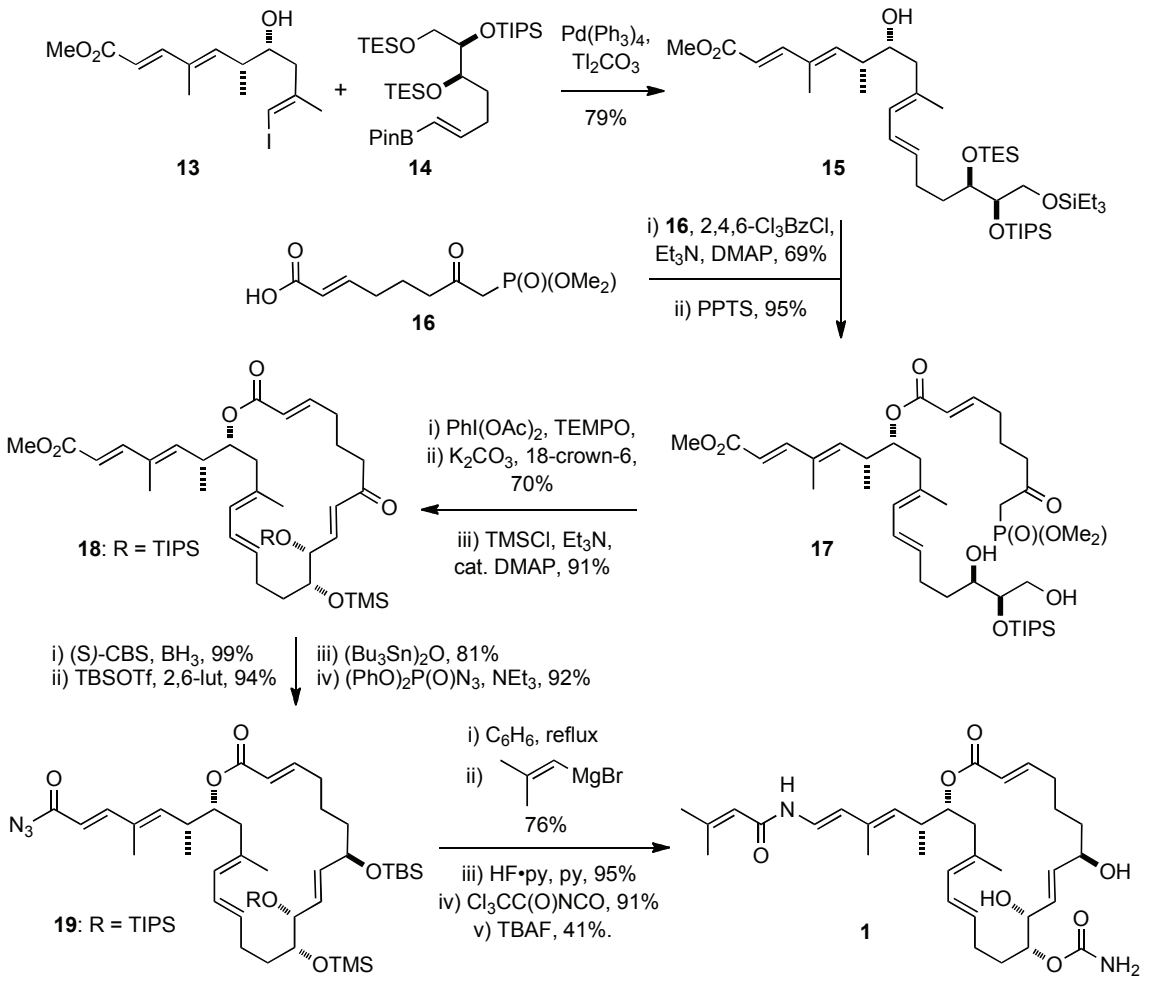
1.4 Synthetic studies on palmerolide A

In the six years since the discovery of the palmerolides, a number of approaches to the synthesis of palmerolide A (**4**), have been reported.[5-8] The first synthesis of **1** with the incorrect structure was accomplished by De Brabander's group.[5] They then revised the stereochemical assignment proposed by Baker in the isolation paper to **4** and validated this by total synthesis. Shortly after the first synthesis, Nicolaou and Chen reported their approach towards the natural palmerolide A **4** and its analogues.[6] Hall accomplished the next total synthesis of **4**.[8] Following these investigations several formal synthetic efforts have been published.[22-29] The successful approaches are presented herein.

1.4.1 The first synthesis of palmerolide A by De Brabander

In 2007 De Brabander and co-workers synthesised the proposed structure of palmerolide A (**1**). Their strategy relied on a Suzuki coupling[30] of vinyl iodide **13** and vinylboronate **14** to construct the advanced diene **15** (Scheme 1.4.1). Yamaguchi esterification with fragment **16**[31] and subsequent silyl deprotection gave diol **17**. Selective oxidation[32] of the primary alcohol, followed by an intramolecular Horner-Wadsworth-Emmons (HWE) macrocyclisation[33] and subsequent silyl protection gave macrolactone **18**. Corey-Bakshi-Shibata reduction of the enone **18** introduced the C7 stereocentre,[34] which was subsequently protected as the TBS ether. Ester hydrolysis[35] and formation of azide **19** set the stage to introduce the enamide side chain. Curtius rearrangement of **19** and trapping of the intermediate isocyanate with 2-methyl propenylmagnesium bromide completed the enamide side chain. Selective TMS deprotection at C11 allowed for the introduction of the carbamate. Global deprotection furnished the target molecule **1**. Unfortunately, the NMR data was inconsistent with the reported ^{1}H and ^{13}C spectra of palmerolide A, indicating that the initial stereochemical assignment was incorrect. After thorough investigation, De Brabander chose to invert the configuration of the C19-C20 centres of the initially synthesised isomer **13** and subject it to the developed synthetic strategy. Gratifingly, the NMR spectra and remaining analyses matched the data reported for palmerolide A. However, the CD spectra of the synthetic and natural compounds were mirror images. Ultimately, the synthesised structure proved to be the *ent*-palmerolide A (**4**) and allowed the definition of the absolute stereochemistry of the natural product. The total synthesis of

4 was completed in thirty-three steps, with a longest linear sequence of 23 steps and 2.9% overall yield.

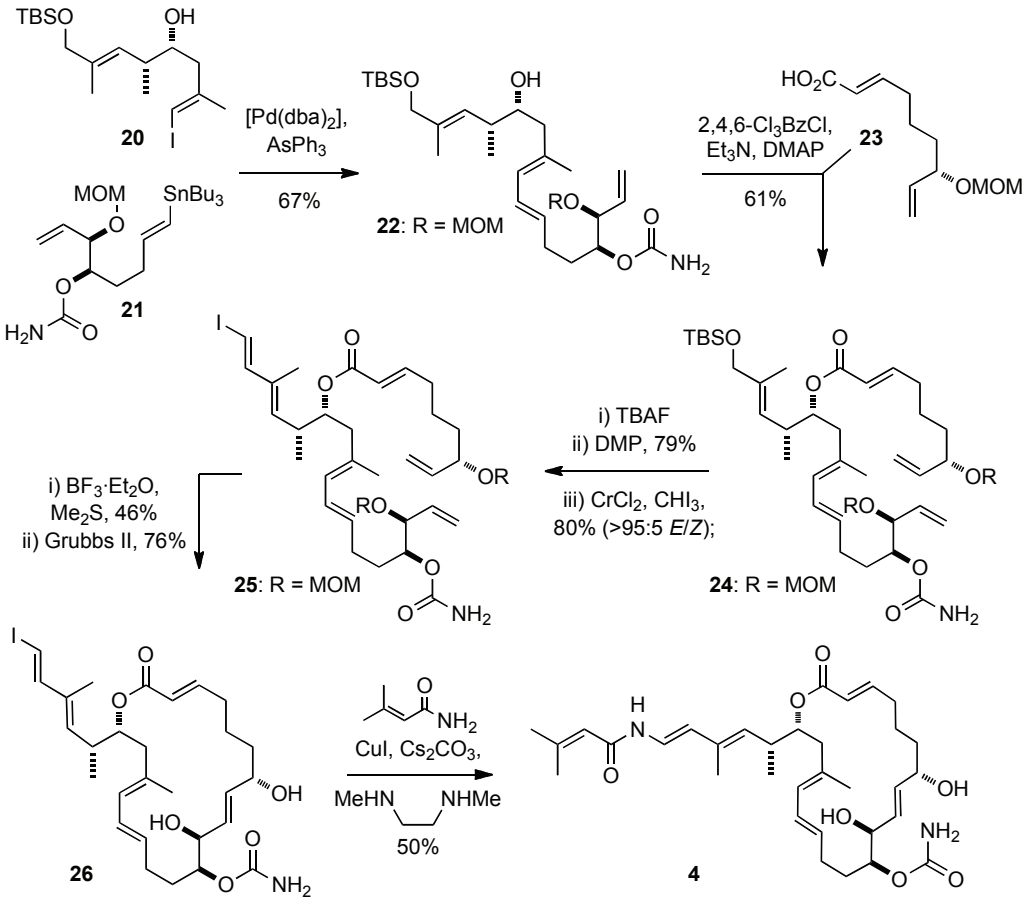


Scheme 1.4.1 Synthesis of the initially proposed structure of palmerolide A by De Brabander.

1.4.2 Nicolaou and Chen synthesis of palmerolide A

Shortly after De Brabander published the synthesis of *ent*-palmerolide A, Nicolaou and Chen presented their approach towards palmerolide A (**4**).[6] Their strategy for the assembly of the key subunits began with Stille coupling between vinyl iodide **20** and vinyl stannane **21** providing tetraene **22** (Scheme 1.4.2).[36] Carboxylic acid **23** was esterified with alcohol **22** under Yamaguchi conditions to give ester **24**.[31] Subsequent desilylation and oxidation set the stage for Takai olefination to introduce the vinyl iodide.[37] Removal of the two MOM groups from **25** gave the intermediate diol, which underwent ring-closing metathesis to form a macrocycle **26**. The installation of the enamide moiety was achieved through the application of a Buchwald Cu(I)-mediated coupling,[38] completing the synthesis

of **4**. The synthesis of the naturally occurring palmerolide A **4** was achieved in 28 steps, with a longest linear sequence of 15 steps and 1.7% overall yield. Thereafter, Chen published the complete synthetic efforts towards the palmerolide A,[7] followed by the synthesis of analogues, which were subsequently subjected to further SAR studies.[39,40]

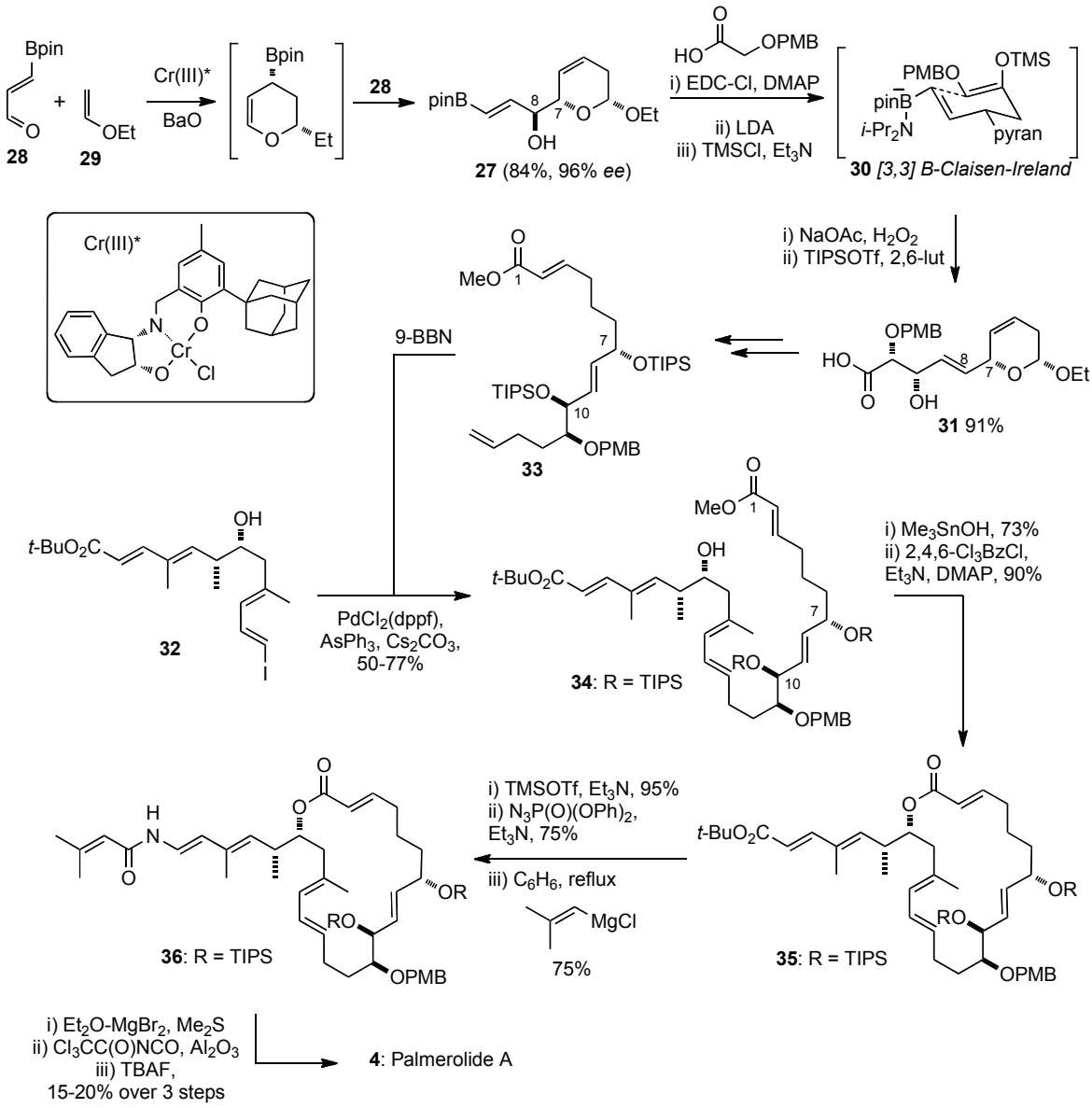


Scheme 1.4.2 Synthesis of natural palmerolide A by Nicolaou and Chen.

1.4.3 Hall synthesis of palmerolide A

The Hall approach utilised his organoboron methodology to construct the advanced intermediates (Scheme 1.4.3). At first, fragment **27** was formed using a [4+2] hetero-Diels-Alder reaction of **28** and **29**,[41] followed by allylboration and subsequent [3,3] Ireland-Claisen rearrangement of the alkenylboronate **30** to form **31**.[42] The left side of the molecule, C14-C25 subunit **32** was accessed by applying enantioselective crotylboration methodology where a tin tetrachloride-based catalyst, developed within the Hall group, was used to install the C19/C20 stereocentres.[43] Coupling of the fragments **32** and **33** was accomplished *via* a boron-alkyl Suzuki reaction providing access to the advance intermediate **34**. Hydrolysis of the methyl ester with a trimethyltin hydroxide and

subsequent macrolactonisation under Yamaguchi conditions delivered macrolactone **35**. Introduction of the enamide side chain providing **36** was accomplished following De Brabander's approach *via* Curtius rearrangement of the azide, which was installed after *tert*-butyl ester hydrolysis. Cleavage of the PMB group and carbamate formation at C11 preceded final deprotection with TBAF, which completed the natural palmerolide A (**4**).

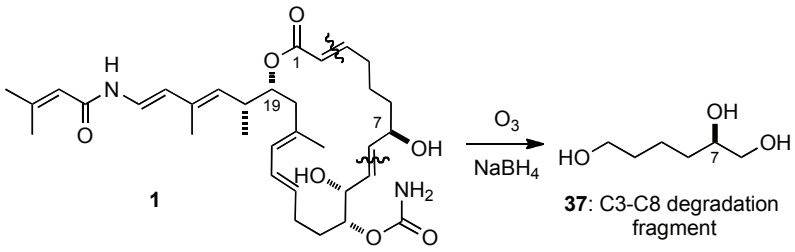


Scheme 1.4.3 Synthesis of natural palmerolide A by Hall.

1.5 Methods for the determination of the absolute stereochemistry in complex molecules

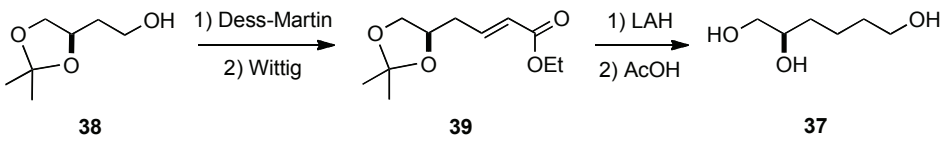
1.5.1 Degradation studies to confirm the absolute stereochemistry of palmerolide A

Following the stereochemical re-assignment of palmerolide A by the first synthesis, Baker and co-workers re-investigated their data for the initially proposed structure **1**. In order to clarify all uncertainty, they employed another powerful method used in determination of the absolute stereochemistry of complex molecules. Degradation studies were undertaken to access fragments of the natural palmerolide A with questionable stereochemistry. This approach was found to be a viable method for solving the stereochemical errors in **1**.[44] Their strategy used reductive ozonolysis to access the C3-C8 fragment **37** of palmerolide A, with the ambiguous C7 stereocentre (Scheme 1.5.1). The obtained data for the 1,2,6-hexanetriol **37** was then compared to the literature records for (*R*)-1,2,6-hexanetriol[45] revealing an inconsistency in the optical rotation values, both in magnitude and sign.



Scheme 1.5.1 Degradation studies of the palmerolide A.

Therefore, they decided to prepare synthetic (*R*)-1,2,6-hexanetriol **37** starting from the (*R*)-acetonide of 1,2,4-trihydroxybutane **38**. Following a sequence of Wittig reaction, reduction of enoate **39** and subsequent deprotection gave (*R*)-1,2,6-hexanetriol (Scheme 1.5.2), which identity was confirmed by spectroscopic and spectrometric analysis. However, comparison of the optical rotation in methanol for synthetic (*R*)-1,2,6-hexanetriol (+11.1) with the optical rotation of the natural C3-C8 degradation fragment **37** (-9.0) revealed they were opposite in sign, providing evidence for the C7 centre being (*S*)-configured.



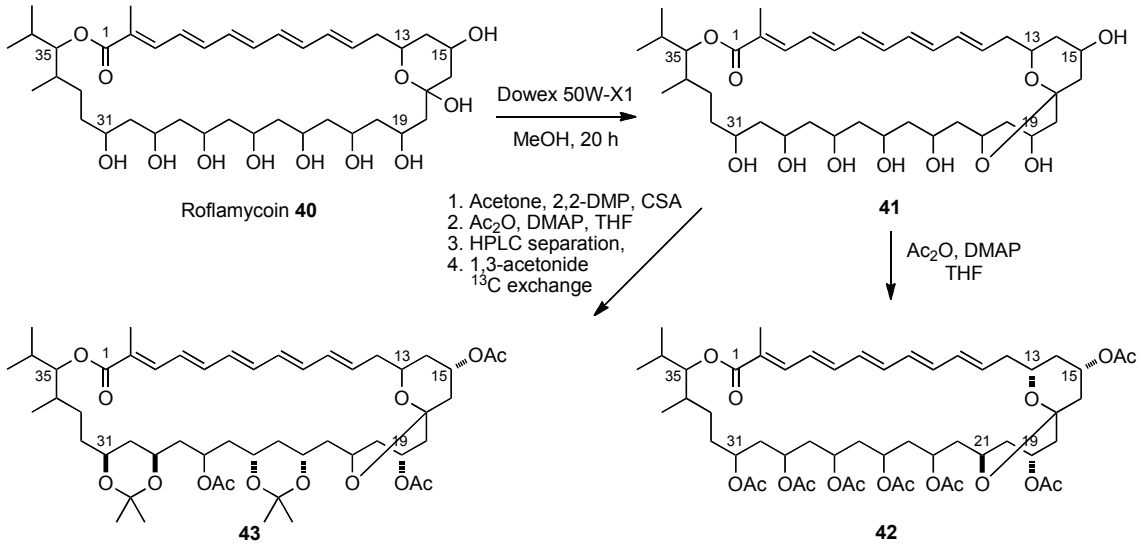
Scheme 1.5.2 Synthesis of the (*R*)-degradation fragment 37.

To provide a final proof, the synthesis of the *ent*-degradation fragment **37** starting from the (*S*)-acetonide of 1,2,4-trihydroxybutane was carried out. In this case, the optical rotation of the (*S*)-triol (-11.6) matched the optical rotation of the degradation product of the natural sample (-9.0) confirming the absolute stereochemistry of the C7 centre of the palmerolide A bearing (*S*)-configuration.

1.5.2 Degradation studies in determining the absolute stereochemistry of complex molecules

The synthesis of degradation fragments of complex molecules is a well-established technique enabling the elucidation of relative and absolute stereochemistry. It is often applied when spectroscopic experiments fail to provide unambiguous information, crystallographic data is not accessible and chemical derivatisation is difficult. However, the presence of functionalities susceptible to controlled fragmentation is essential for making this approach viable.

This technique is well documented in the literature and provides a practical handle for addressing stereochemical issues prior to embarking on the total synthesis.[46] Rychnovsky employed this approach to determine the relative and absolute stereochemistry of roflamycoin **40** (Scheme 1.5.3), a polyketide macrolide antibiotic consisting of repeating 1,3-diol motifs with 2048 possible stereoisomers.[46] This remarkable work comprises most of the techniques available for a synthetic chemist to establish the stereo-structure of a complex molecule. The relative stereochemistry of **40** was determined based on the combination of the chemical derivatisation studies and spectroscopic techniques (Scheme 1.5.3). The arrangement of C13/C15 and C19/C21 was found to be *anti* upon the inspection of the ^{13}C NMR data obtained for the derivative **41**. Based on these findings, next derivative **42** was studied and provided evidence by ^{1}H NMR and nOe experiments of the *syn* relation of C15/C19 stereocentres. The ^{13}C-enriched compound **43** showed ^{13}C NMR signals consistent with the *syn* relative configuration of the C23/C25 and C29/C31 stereocentres in the acetonides.



Scheme 1.5.3 Assignment of the relative configuration of the fungal metabolite roflamycoin 40 by chemical derivatisation and ^{13}C NMR spectroscopic analysis.

This observation was supported by the earlier studies within the Rychnovsky group,[47,48] where ^{13}C-NMR spectroscopic data for a wide range of 1,3-diol acetonides were investigated (Figure 1.5.1). Due to the conformational preferences of *syn* and *anti* diol acetonides, their methyl and acetal carbons appear at particular chemical shifts in their respective ^{13}C NMR spectra. Their analysis revealed, that 1,3-*syn* acetonides prefer to adopt chair like conformation, resulting in a specific ^{13}C resonances at 19 and 30 ppm for methyl groups and 98 ppm for acetonide. In comparison, the 1,3-*anti* acetonides were found to favour a twist-boat conformation with ^{13}C resonances at 23, 25 and 100 ppm for respective carbons.

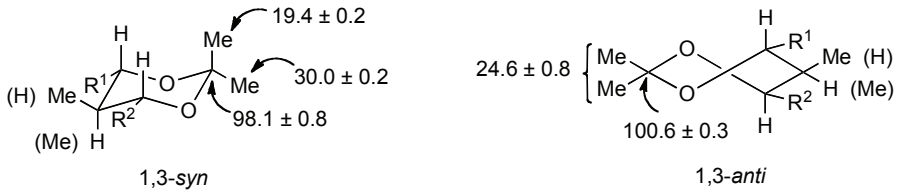
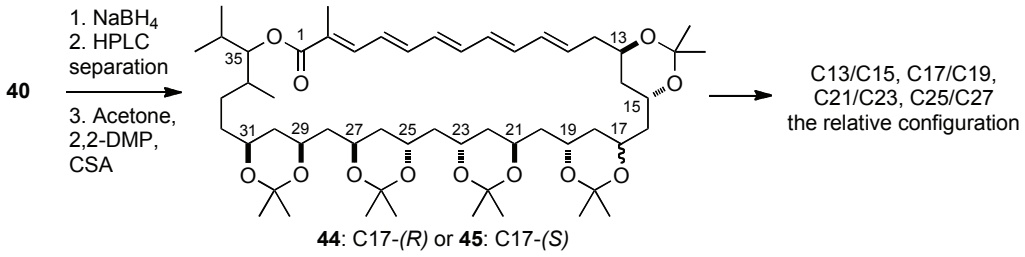


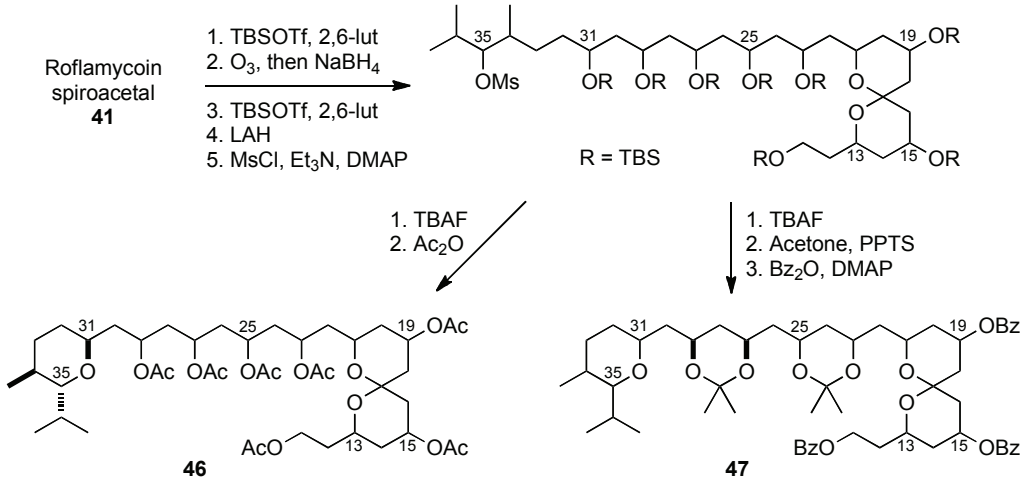
Figure 1.5.1 ^{13}C shifts in 1,3-*syn/anti* acetonides.

Reduction of the hemiacetal of **40** gave a mixture of C-17 epimers (Scheme 1.5.4), which were separated by chiral HPLC and further protected to furnish the acetonides **44** and **45**. Spectroscopic analysis of **44** and **45** established the *anti* relationships at the C13/C15, C21/C23, and C25/C27 stereocentres.



Scheme 1.5.4 Derivatisation of roflamycoin 40.

To determine the relative stereochemistry of the C27/C29, C31/C34, and C34/C35 centres the parent molecule **40** was subjected to degradation studies (Scheme 1.5.5). The polyene fragment was cleaved by ozonolysis and subsequent sodium borohydride reduction provided access to the advanced intermediate. Following sequence of synthetic operations resulted in the formation of peracetylated spiro-acetal **46** enabling the assignment of the pyran C31, C34 and C35 stereocentres. In conjunction with spectroscopic data, computer modeling was employed to elucidate the relative *syn* stereochemistry at C31/C34 and C34/C35 centres. In order to find the final relative relationship of C27/C29, degradation fragment **47** was prepared. The analysis of the NMR data proved the relative stereochemistry of C27/C29 to be *syn*.

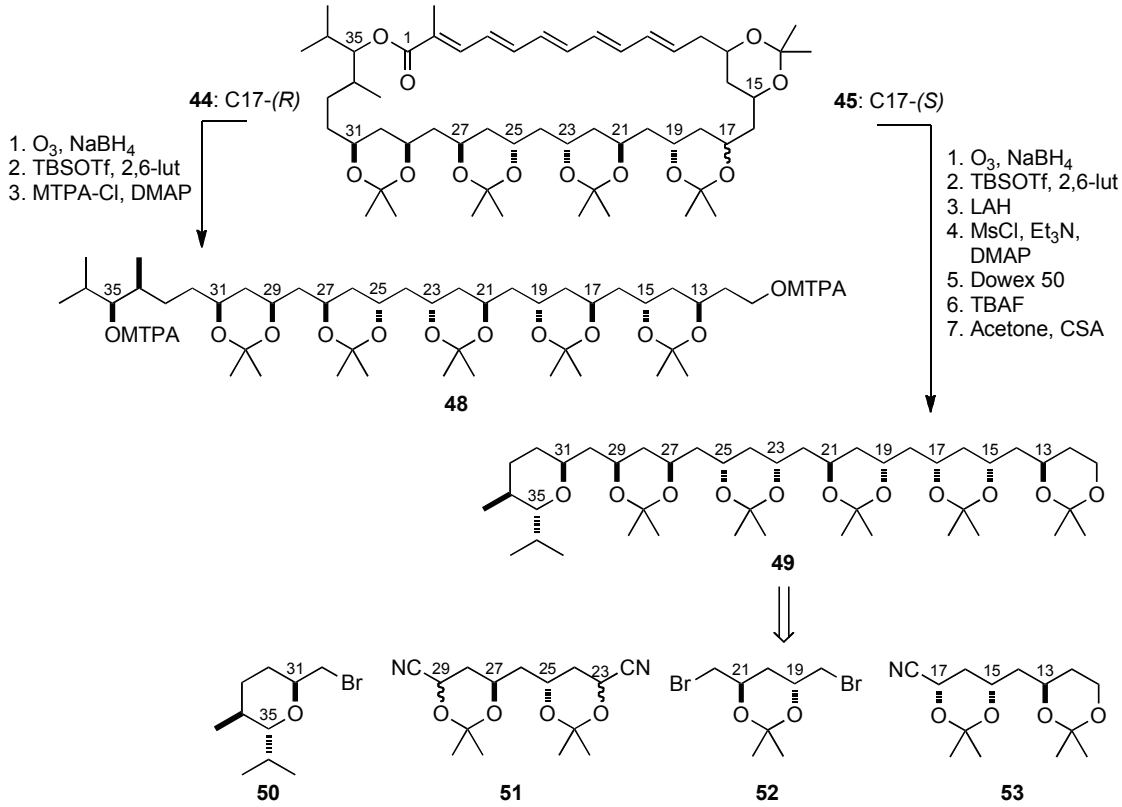


Scheme 1.5.5 Assignment of the relative configuration by degradation fragment studies.

The relative stereochemistry assigned so far was confirmed by analysis of the ^{13}C-enriched compound **48**, which NMR showed presence of the one *anti* and four *syn* acetonides as established previously (Scheme 1.5.6). Determination of the absolute

stereochemistry of roflamycoin **40** was achieved by preparation of the Mosher ester derivatives of the C35 hydroxyl of the advanced degradation fragment **48** derived from **44** (Scheme 1.5.6). Detailed analysis according to the Mosher method confirmed the *S* configuration of the C35 stereocentre. Rychnovsky decided then to synthesise degradation fragment **49** instead of the entire molecule **40**, as **49** contains the entire stereostructure.

The synthetic approach to **49** was based on the cyanohydrin and bromo-acetonide building blocks (**50**, **51**, **52**, **53**) developed within the Rychnovsky group (Scheme 1.5.6). Their strategy involved the coupling of these pieces using standard alkylation chemistry followed by a stereoselective reductive de-cyanation to give pentaacetonide **49**.[46] Final comparison of the synthetic and natural material by ^{1}H NMR, ^{13}C NMR, HRMS, and TLC showed identical parameters, verifying the relative and absolute stereochemistry of roflamycoin **40** as in the fully protected fragment **49**.



Scheme 1.5.6 Assignment of the absolute stereochemistry by Mosher ester analysis and a synthesis of the degradation fragment 49.

1.5.3 *J*-based configurational analysis developed by Murata

Traditional NMR methods provide very reliable information for the elucidation of the planar structure. However, configurational analyses often require a combination of various techniques. A method for the determination of the relative configuration of adjacent stereocentres was recently developed by Murata[49] and instantly has found wide interest and application in establishing the stereochemistry of complex natural products. This method is based on a detailed investigation of hetero- and homo-nuclear spin-coupling constants ($^{2,3}J_{C,H}$ and $^{3}J_{H,H}$). Commonly employed nOe-based techniques are not reliable in assigning the stereochemistry of highly flexible carbon chains. The observed signal intensities are affected by the presence of multiple conformers, where even minor populations could have a disproportionately large effect, leading to incorrect interpretations. In these systems with conformational flexibilities, the observed coupling constants exist as a weighted average of those associated with each conformer, consequently the most populated one will dominate. Correlation of the vicinal protons spin-couplings ($^{3}J_{H,H}$) depends on the dihedral torsion angle and is described using the Karplus equation. Vicinal carbon-proton spin-coupling constants ($^{3}J_{C,H}$) also follow a Karplus-type relationship and complements the stereochemical information obtained from $^{3}J_{H,H}$. Additional information from $^{2}J_{C,H}$ further expands the utility of the coupling constants in the configurational analysis (Figure 1.5.2). Advances in the instrumentation and spectroscopic techniques facilitated the calculation of more accurate values of the coupling constants in complex molecules, making the method highly reliable.[50]

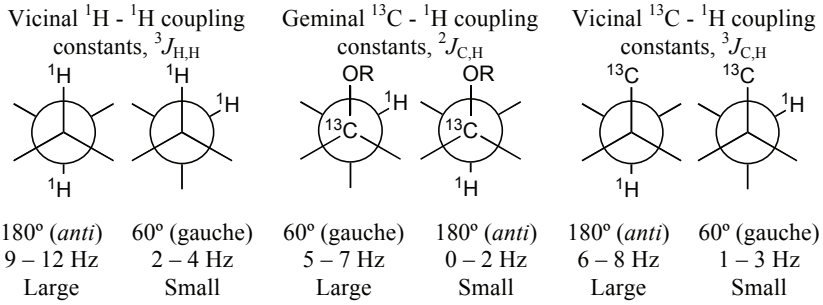


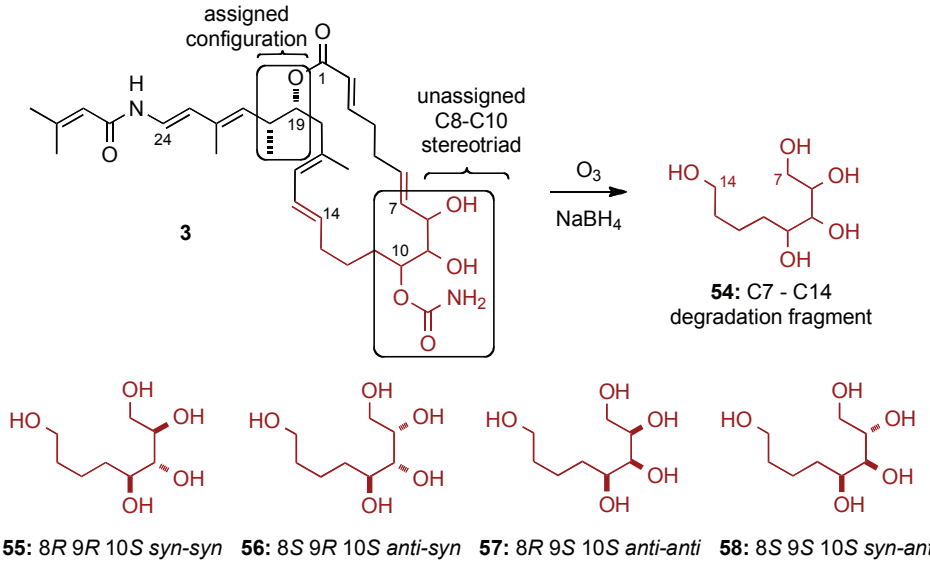
Figure 1.5.2 Coupling constant size dependence on dihedral angle.

This method was applied to establish the configuration of palmerolide A **1**.[3,4,21] Although it provided a great amount of detailed conformational information the absolute configuration was affected by the incorrect interpretation of the MTPA-esters.

1.6 Retrosynthetic strategy for palmerolide C

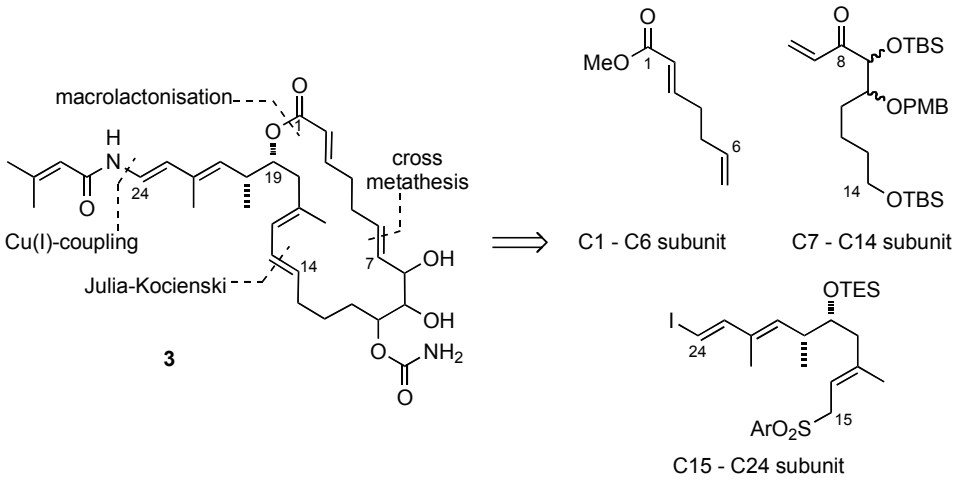
As part of our programme to develop efficient synthetic strategies towards potential drug candidates we embarked on a journey into the total synthesis of palmerolides. This family of marine polyketides with unique chemical and biological properties have already entered the drug discovery arena, however still remaining relatively unexplored. Our contribution towards the studies on palmerolides unveils a detailed investigation of the stereostructure of palmerolide C (**3**) together with a convergent synthetic approach culminating in the total synthesis of the proposed structure.

The focus was initially set on the elucidation of the relative and absolute stereochemistry of palmerolide C (**3**). Due to the stereochemical uncertainty of the contiguous C8-C10 stereocentres, this would impose the potantial synthesis of up to sixteen different isomers of the natural product. Drawing from the previous studies on palmerolide A (**4**), where the absolute stereochemistry was verified by the synthesis of one of the degradation fragments,[44] we decided to follow a similar approach. Using olefins as the functional handles, **3** would be cleaved by ozonolysis and subsequent reduction to provide poly-hydroxylated fragment **54** (Scheme 1.6.1). The synthesis of diastereomeric degradation fragments (**55-58**) would then become the primary goal of this project. The relative and absolute stereochemistry would then be defined in collaboration with Professor Bill Baker (University of South Florida, USA) by detailed comparison of the spectroscopic and specific rotation data of the synthetic and natural fragments.



Scheme 1.6.1 Strategy towards stereochemical assignment of the relative and absolute configuration of palmerolide C (3).

Following this phase, our focus would be the synthesis of the diastereoisomer identified in the degradation fragment studies and the incorporation of the required subunit into a convergent synthetic strategy outlined in Scheme 1.6.2. Initial retrosynthetic disconnection of the C24 and enamide functionality revealed the carbon framework of palmerolide C (**3**), which was divided into three key segments after the opening of the macrolactone. The assembly of the C6-C7 and C14-C15 olefins was envisaged to arise from cross-metathesis and Julia-Kocienski olefination, respectively.

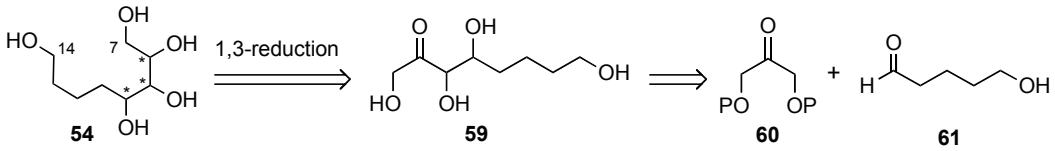


Scheme 1.6.2 Retrosynthesis and degradation fragment of palmerolide C (3).

Chapter 2

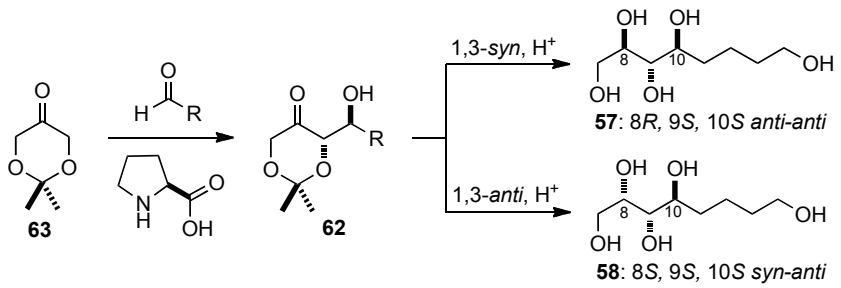
2.1 Synthesis of C7-C14 degradation fragments

The determination of the relative and absolute stereochemistry of the natural C7-C14 degradation fragment **54** would require the synthesis of a minimum of four diastereomeric poly-hydroxylated compounds for spectroscopic comparison. We reasoned that such hydroxylated compounds could be obtained from the 1,3-stereocontrolled reduction of aldol products of type **59**, which in turn could arise from dihydroxyacetone-derived building block **60** and a suitable aliphatic aldehyde **61** *via* organocatalysis (Scheme 2.1.1).



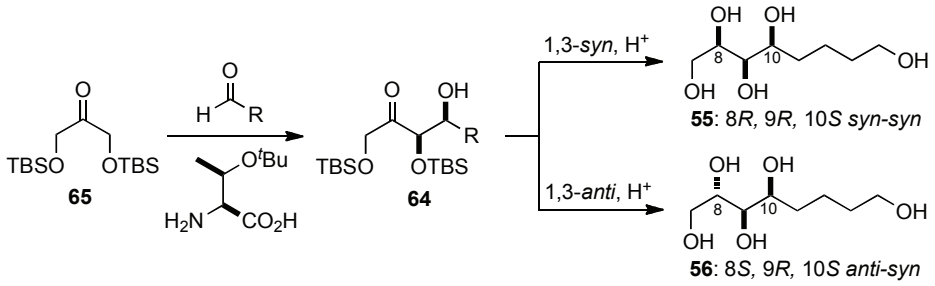
Scheme 2.1.1 Retrosynthesis of the degradation fragment 54.

In construction of the 9,10-*anti* aldol product **62** methodology developed by Enders[51] would be explored where (*S*)-proline is used in aldol reaction between 2,2-dimethyl-1,3-dioxane-5-one (dioxanone) **63** and an aldehyde. Following substrate directed 1,3-*syn* and 1,3-*anti* reduction, this would provide access to the two degradation fragments **57** and **58** (Scheme 2.1.2).



Scheme 2.1.2 Synthetic strategy to construct *anti-anti* and *syn-anti* products.

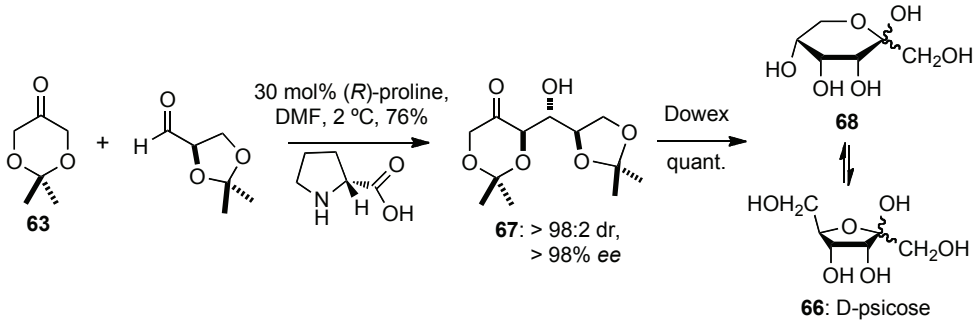
An organocatalytic approach would also be explored in the corresponding 9,10-*syn* series towards **64**, where O-*t*-Bu-threonine-catalysed aldol reaction developed by Barbas would serve as a primary event involving dihydroxyacetone derivative **65**. Remaining degradation fragments **55** and **56** (Scheme 2.1.3) would be completed applying the same approach developed in the 9,10-*anti* series.



Scheme 2.1.3 Synthetic strategy to construct *syn-syn* and *anti-syn* products.

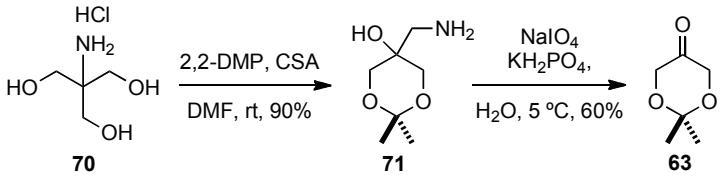
2.2 Construction of the 9,10-*anti* aldol

To test the viability of our strategy for the synthesis of fragment **54**, work commenced with the construction of a system for the cross-aldol condensation. One-step syntheses of poly-oxygenated motifs utilising organocatalytic transformations have been extensively studied over the past decade.[51-53] Enders and Grondal utilised the proline-catalysed aldol reaction to effectively synthesise D-psicose (**66**) with excellent diastereo- and enantio-control over the newly formed stereogenic centres (Scheme 2.2.1). Their optimised conditions employed 30 mol% of (*R*)-proline, equimolar amount of substrates in dimethylformamide. The reaction mixture was then stored at 2 ºC for a period of six days. Upon cleavage of the acetonides in **67** cyclisation was induced to furnish a mixture of α,β-D-psicofuranose **66** and α,β-D-psicopyranose **68**.[51]



Scheme 2.2.1 Organocatalytic formation of D-psicose.

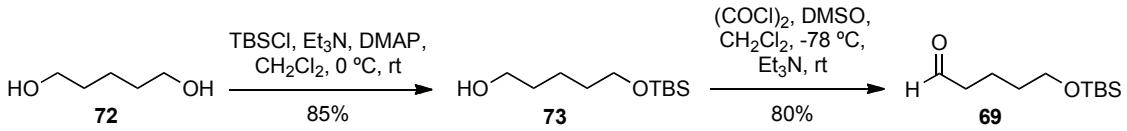
Guided by the reported examples, we embarked on the investigation of the (*S*)-proline-catalysed cross aldol reaction between the dioxanone **63** and aldehyde **69**. Ketone **63** was readily prepared in a two-step procedure from commercially available Trizma® salt **70**. Formation of the 1,3-acetonide **71** followed by oxidative cleavage with sodium periodate furnished ketone **63** in good overall yield (Scheme 2.2.2).



70 **71** **63**

Scheme 2.2.2 Ketone 63 preparation for proline catalysed aldol reaction.

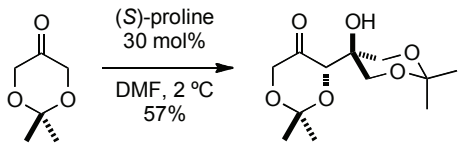
Preparation of aldehyde **69** started with the mono-silyl protection of 1,5-pentanediol **72**. Subsequent oxidation of **73** under Swern conditions afforded aldehyde **69** in 68% yield over two steps (Scheme 2.2.3).



72 **73** **69**

Scheme 2.2.3 Preparation of the aldehyde 69.

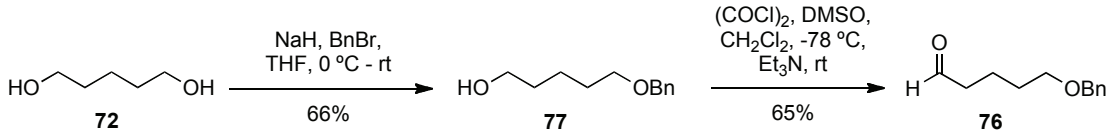
Under Enders' conditions (dioxanone **63** 1 eq, 30 mol% (*S*)-proline, aldehyde **69** 1 eq, DMF 1.9 M, 6 days at 2 ºC) formation of the aldol product **74** was not detected,[51] but instead self-condensation of ketone **63** was observed (Table 2.2.1, entry 1). Enders also reported this side reaction, where in absence of the aldehyde dioxanone **63** reacts with itself to form protected (*S*)-dendroketose **75** in 57% yield (Scheme 2.2.4).



63 **75** 94% *ee*

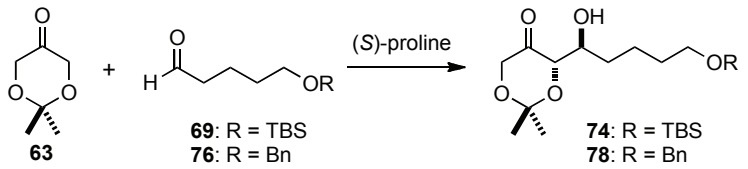
Scheme 2.2.4 Formation of protected (*S*)-dendroketose.

Further investigations into catalyst loading and substrate equivalents did not deliver the desired product **74**. In addition, solvent and temperature were screened. Unfortunately none of the performed operations led to the formation of the cross-coupled product **74**. However, upon changing the protecting group of the aldehyde **69** to **76**, which was readily prepared in two steps from **72** *via* mono protection with BnBr, followed by Swern oxidation of **77** in 43% overall yield (Scheme 2.2.5), the desired aldol product **78** was isolated, albeit in a low 19% yield (Table 2.2.1, entry 2).



Scheme 2.2.5 Formation of the aldehyde 76.

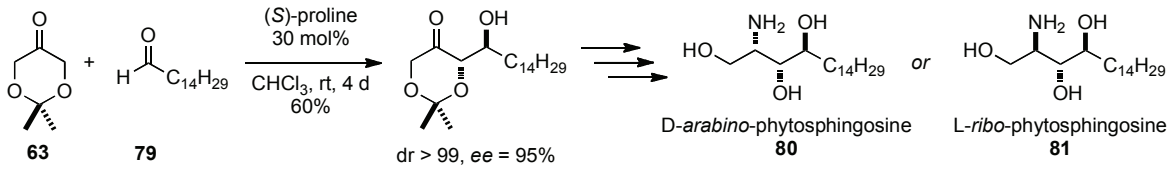
Upon attempts to optimise the reaction conditions **78** was formed in only 23% yield after carrying out the reaction at room temperature. However, long reaction times and a range of side products in the attempted cross-aldol reactions prompted a search for a suitable aldehyde compatible with an organocatalytic approach.



Entry	R	Conditions	Yield (%)
1	TBS	30 mol% cat, DMF, 2 °C	---
2	Bn	30 mol% cat, DMF, 2 °C	19
3	Bn	30 mol% cat, DMF, rt	23

Table 2.2.1 *(S)*-proline-mediated aldol reaction.

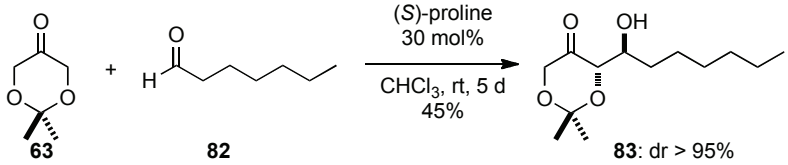
Encouragingly, Grondal and Enders have provided an example of proline catalysed aldol reaction where the pentadecanal **79** was employed in the synthesis of sphingoids **80** and **81** (Scheme 2.2.6).[54] They found that critical to that system was the nature of solvent and temperature. The best results were obtained when the reaction was performed in chloroform at room temperature for four days (60% isolated yield, > 99:1 dr, 95% *ee*).



63 79 80 81

Scheme 2.2.6 Synthesis of sphingoids using proline aldol.

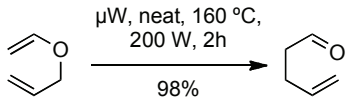
With their findings in mind, unbranched heptanal **82** was used in the reaction with dioxanone **63** and (*S*)-proline (30 mol%) in chloroform. Gratifyingly, the cross-aldol product **83** was isolated as a single diastereoisomer in 45% yield after storing the reaction for five days at room temperature (Scheme 2.2.7). The apparent difference between the initially examined system and the revised reaction with heptanal **82**, was not only the solvent, but also the unexplained influence of the terminal oxygenation of the aldehydes **69** and **76** in the cross-aldol reaction.



63 82

Scheme 2.2.7 Formation of the aldol product 83 catalysed by *(S)*-proline.

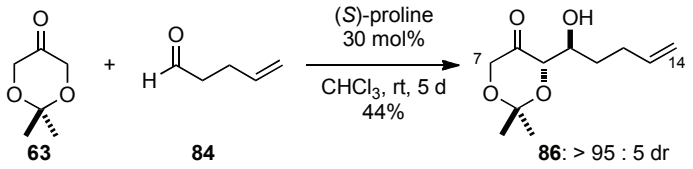
Having established the viability of the proline-catalysed system, 4-pentenal **84** was deemed a suitable precursor for the introduction of the terminal C14 hydroxyl functionality at a later stage of the synthesis. 4-Pentenal **84** was readily accessed *via* Claisen rearrangement of allyl vinyl ether **85** under microwave irradiation (Scheme 2.2.8).[55]



85 84

Scheme 2.2.8 Claisen rearrangement of the allyl vinyl ether 85.

Aldehyde **84** was then added at room temperature to a mixture of ketone **63** and 30 mol% (*S*)-proline in chloroform (Scheme 2.2.9). After five days the desired aldol adduct **86** was isolated in 44% yield with excellent diastereoselectivity (>95:5 dr).



Scheme 2.2.9 Formation of the aldol product 86.

2.2.1 Determination of the absolute configuration at C10 stereocentre

To establish the absolute configuration at the newly formed C10 stereocentre and determine enantiomeric purity of **86**, the respective (*R*)- and (*S*)-Mosher esters **87** and **88** were prepared. The derivatisation with chiral reagents such as α-methoxy-α-trifluoro-methylphenyl acetic acid (MTPAA or Mosher's acid) is an established method for the assignment of the absolute configuration of secondary alcohols and amines by ^{1}H NMR spectroscopy. It was introduced in 1973 by Mosher *et al.*[56] The presence of a defined chiral group (*i.e.* aromatic) in the derivatising reagent induces an anisotropic effect on the covalently bound secondary alcohol. Depending on the absolute configuration of the reagent, the planar arrangement of the trifluoromethyl and carbonyl groups with the hydrogen of the carbinol centre, the substituents are shielded/deshielded accordingly to the aromatic group present (Figure 2.2.1). The shielding/deshielding can be measured by ^{1}H NMR spectroscopy. In addition, ^{19}F NMR can be used to determine the enantiomeric excess as the (*S*)- or (*R*)-MTPA esters give rise to two distinct signals for derivatised enantiomers.

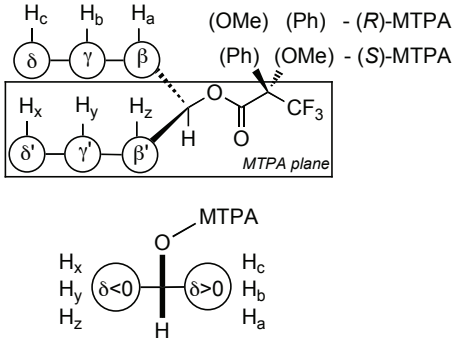
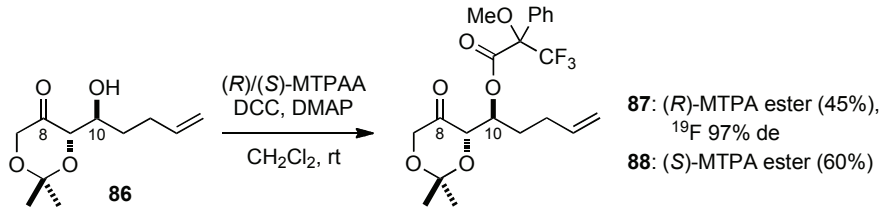


Figure 2.2.1 Preferred conformations of the (*S*)-MTPA and (*R*)-MTPA esters of 86 in $CDCl_3$.

Analysis of the ^{1}H NMR and ^{19}F NMR spectra of the (*R*)- and (*S*)-MTPA esters **87** and **88** were conducted according to the advanced Mosher method.[57] The experimental

data correlated with the expected 10*S* configuration shown in **86**, the MTPA-aromatic group shielded protons placed on the same face H10-H14 (H_x, H_y, H_z in Figure 2.2.1) in the (*S*)-MTPA ester **88** as evident by ^{1}H NMR spectroscopy. Consequently, the phenyl group in (*R*)-MTPA ester **87** shielded the H7-H9 protons (H_a, H_b, H_c in Figure 2.2.1) situated on the same face. This shielding moves affected protons upfield in the ^{1}H NMR spectrum. The subtraction of the chemical shift values for the particular protons ($\delta_S - \delta_R$) gave negative values in the H10-H14 region and positive in the H7-H9 (Table 2.2.2). Analysis of the data obtained for the (*S*)- and (*R*)-MTPA esters **87** and **88** confirmed the predicted 10*S* configuration and also ^{19}F NMR of **87** (Figure 2.2.2) provided evidence for 97% enantiopurity of **86**.



Assignment	δ_S/ppm	δ_R/ppm	$\delta_S - \delta_R$/ppm
H-7a	4.20	4.13	0.07
H-7b	3.98	3.93	0.05
H-9	4.57	4.43	0.14
H-10	5.48	5.52	-0.06
H-13	5.71	5.76	-0.05
H-14	4.95	5.01	-0.05

Table 2.2.2 ^{1}H NMR analysis of the (*R*)- and (*S*)-MTPA esters of β-hydroxy ketone 86.

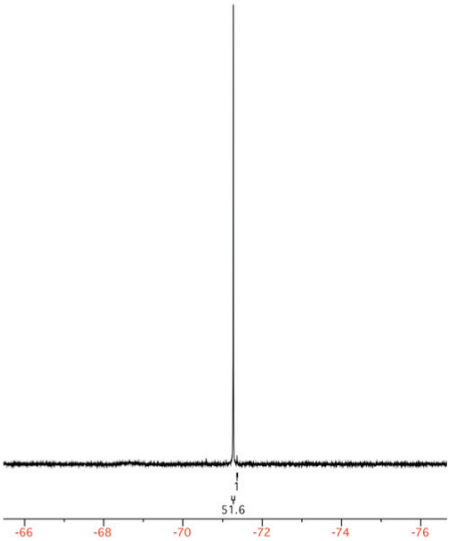
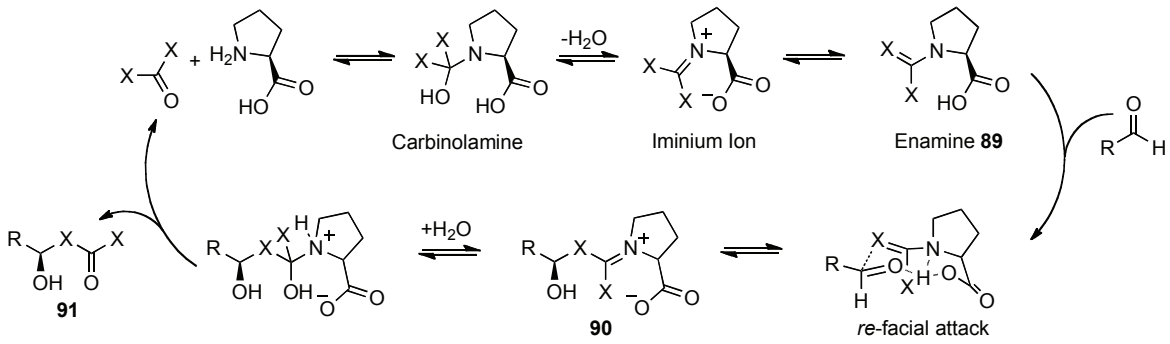


Figure 2.2.2 ^{19}F NMR of the (*R*)-MTPA ester 87.

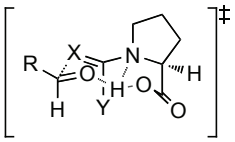
2.2.2 Mechanism of proline-catalysed aldol reaction

The mechanistic aspects of the proline-catalysed transformations have been widely studied.[58-60] The high levels of enantioselectivity obtained in aldol reactions with this amino acid is attributed to its pyrrolidine ring, which upon treatment with a carbonyl compound forms the enamine **89**. Iminium ion **90**, formed by attack of the enamine on the *re*-face of the aldehyde is subsequently hydrolysed to afford chiral β-hydroxyketone **91**.[60] The proposed reaction mechanism (Scheme 2.2.10) was initially based on the established mechanism of class-I aldolases,[61] which proceed *via* similar intermediates. In addition, density functional theory (DFT) calculations[62] supported the hypothesis of this analogy.



Scheme 2.2.10 Mechanism of (*S*)-proline-catalysed aldol reaction.

The proposed transition state **TS I** illustrates (Figure 2.2.3) that in the aldol reaction, the enamine attack occurs on the *re*-face of the aldehyde. This facial selectivity is dictated by minimising steric interactions between the substituents on the aldehyde and enamine (Figure 2.2.3). Moreover, hydrogen transfer between the carboxylate on proline and the oxygen of the aldehyde controls the enantioselectivity by directing which face of the enamine attacks the aldehyde. One of the most attractive features of proline-catalysed aldol reactions is that both D- and L-proline are readily available, so both enantiomeric products can be accessed. DFT calculations supported the proposed transition state shown in Figure 2.2.3, **TS I**. Based on these calculations it was postulated that an N—H hydrogen bond does not lower the energy of transition state **TS I**.[58]

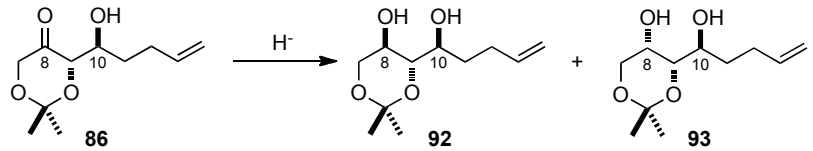


TS I

Figure 2.2.3 Houk's proposed transition state for aldol reaction.

2.2.3 Reduction of the 9,10-*anti* aldol product 86

With the 9,10-*anti* aldol product **86** in hand, the investigation of the substrate-directed 1,3-reduction to install the C8 stereocentre commenced with a screening of borohydride reducing agents, which are summarised in Table 2.2.3. Initial reduction of **86** was performed with sodium borohydride and delivered mixture of diols **92** and **93** in good yield with moderate diastereoselectivity (3 : 1), in favour of the 1,3-*syn* product. Considering this result, standard reduction protocols were employed to explore the possibility of directing selectivity. Reduction with zinc borohydride proceeded in 54% yield to give 1,3-*syn* diol **92** in good selectivity (Table 2.2.3, entry 2).



86 92 93

Entry	Conditions	Yield (%)	92 : 93
1	$NaBH_4$, MeOH, -78 ºC	54	3 : 1
2	$Zn(BH_4)_2$, Et_2O, -78 ºC	54	5.2 : 1
3	$Me_4NBH(OAc)_3$, CH_3CN, AcOH, -78 ºC – 0 ºC	56	1 : 1

Table 2.2.3 Studies of the reduction of β-hydroxy ketone 86.

The predominant formation of the 1,3-*syn* product **92** can be explained by the proposed transition state **TS II** shown in Figure 2.2.4. The metal centre coordinates to the free hydroxyl and carbonyl groups placing the molecule in a locked conformation, with hydride attack from a bottom face, giving rise to the formation of 1,3-*syn* diol.

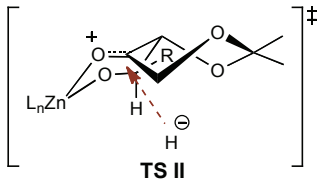


Figure 2.2.4 Transition state for $Zn(BH_4)_2$ reduction.

We then examined Evans'[63] procedure employing $Me_4NBH(OAc)_3$ to exert 1,3-*anti* selective reduction, as extensively documented for acyclic substrates. To our surprise, we did not observe good selectivity (Table 2.2.3, entry 3). We reasoned, supported by earlier studies by Enders[64] that due to the dioxanone unit adopting a twisted boat conformation with the side-chain located in a pseudo-equatorial position, the internal-hydride delivery with preferred axial attack, imposes *syn*-selectivity, as shown in **TS III** in Figure 2.2.5.

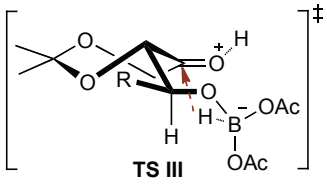


Figure 2.2.5 Enders transition states for 1,3-reduction with $Me_4NBH(OAc)_3$.

In all of the presented reductions, column chromatography on silica gel enabled separation of the diastereomeric diols **92** and **93**. The 1,3-*anti* diol **93** was isolated as a white solid and recrystallisation provided material for a single crystal X-ray analysis (Figure 2.2.6). The acquired data provided evidence for the 1,3-*anti* relation of the diol **93**. In conjunction with Mosher ester analysis of the C10 hydroxyl, the relative and absolute stereochemistry of **93** was established to be 8*S*, 9*S* and 10*S*. Consequently, the corresponding major diastereoisomer **92** had the *anti-anti* arrangement with the 8*R*, 9*S* and 10*S* configuration.

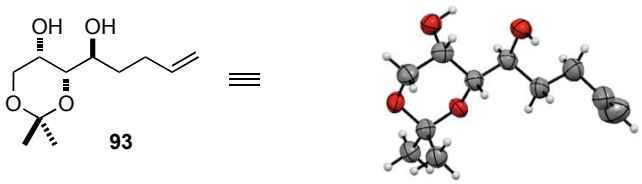
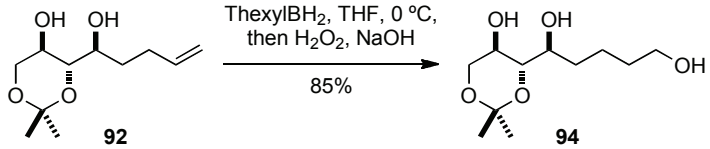


Figure 2.2.6 The 1,3-*anti* diol 93 and ORTEP representation of its solid-state structure.

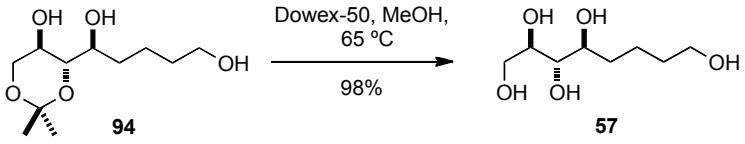
2.2.4 Completion of the 9,10-*anti* series

Having established access to the two required diastereomeric diols **92** and **93**, the introduction of terminal hydroxyl functionality was addressed. The *anti-anti* diol **92** was examined first to find the optimal conditions. Several reagents to introduce the terminal hydroxyl including dimethylsulfide borane (BH_3•SMe_2),[43] 9-borabicyclo-[3.3.1]nonane (9-BBN)[65] and thexyl-borane (thexylBH_2)[66] were tested and it was found that the latter reagent provided the best results, delivering the desired product **94** after oxidative work-up in 85% yield (Scheme 2.2.11).



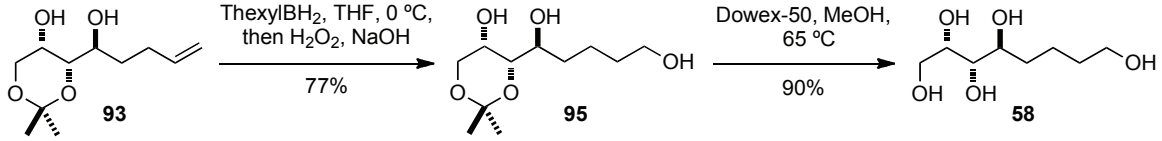
Scheme 2.2.11 Hydroboration to introduce a terminal hydroxyl.

At this point acetonide cleavage would complete the (8*R*, 9*S*, 10*S*)-polyol **57**. Various conditions were investigated to cleave the isopropylidene group including a screen of organic acids such as camphorsulfonic acid, pyridinium-*p*-toluenesulfonate and *p*-toluenesulfonic acid, which all turned out to be ineffective. The isolation of the highly polar product from aqueous work-up was troublesome. Gratifyingly, using acidic Dowex-50 resin, aqueous work-up was eliminated and simple filtration delivered pure product. The resin was first washed with water, 3M HCl and excess methanol before adding to the solution of triol **94** in methanol. When starting material **94** was fully consumed, as indicated by TLC, the suspension was filtered and evaporated to deliver 8*R*, 9*S*, 10*S* *anti-anti* degradation fragment **57** in excellent yield (98%), without the requirement for further purification (Scheme 2.2.12).



Scheme 2.2.12 Dowex-50 resin mediated deprotection.

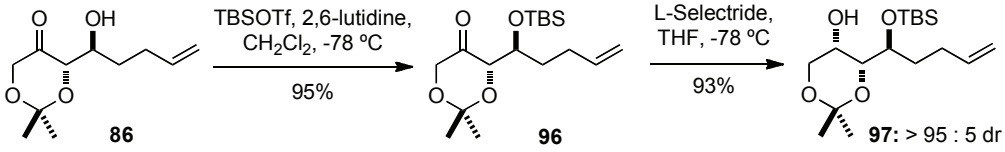
The conditions established for **57** were then applied to the diastereomeric diol **93**. Accordingly, hydroboration with thexylBH$_2$ provided product **93** in 77% yield, following removal of the acetonide protecting group to deliver the diastereoisomeric polyol **58** with the (8*S*, 9*S*, 10*S*) configuration and *syn-anti* arrangement (Scheme 2.2.13).



Scheme 2.2.13 Hydroboration and deprotection providing degradation fragment 58.

2.3 Alternative route to *syn-anti* degradation fragment 58

The difficulties in obtaining the 1,3-*anti* diol **93** were overcome by introducing a bulky TBS protecting group on the free hydroxyl of **86** to form **96** (Scheme 2.3.1). Subsequent reduction with L-Selectride (lithium tri-*sec*-butylborohydride) afforded the 1,3-*anti* product **97**.



Scheme 2.3.1 Direct reduction of the TBS-protected aldol product 96.

The observed selectivity can be rationalised upon consideration of the transition state **TS IV** shown in Figure 2.3.1. The β-OTBS orientating perpendicular to the σ-framework of the carbonyl moiety and minimisation of steric interaction between the R-substituent and the cyclic dioxanone leading to preferential addition of the hydride from the *re*-face of the carbonyl.[67]

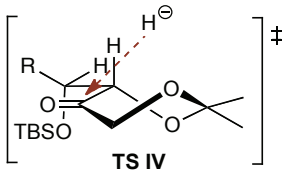
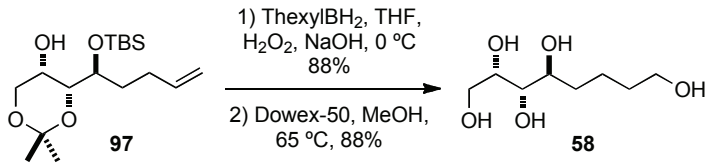


Figure 2.3.1 Enders transition state for a direct hydride delivery in reduction of 96.

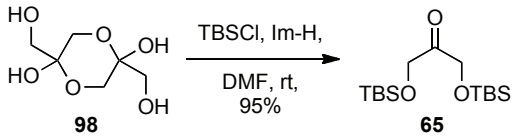
The strategy developed for the synthesis of degradation fragments **57** and **58** allowed for further advancement of the compound **97**. Hydroboration with thexylBH$_2$ delivered intermediate triol in 88% yield (Scheme 2.3.2). The silyl ether and acetonide cleavage was efficiently accomplished using Dowex-50 resin in methanol to provide the *syn-anti* degradation fragment **58** identical to material prepared from **93**.



Scheme 2.3.2 Hydroboration and deprotection providing degradation fragment 58.

2.4 Construction of the 9,10-*syn* aldol *via* an organocatalytic approach

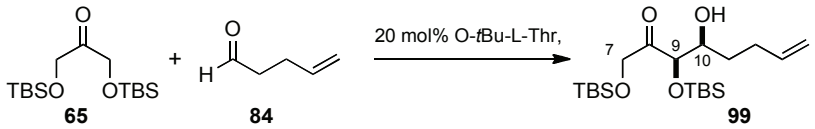
Attention was now directed towards the construction of the second set of diastereomeric degradation fragments **55** and **56** with the 9,10-*syn* configuration. An organocatalytic aldol reaction utilising C3 dihydroxyacetone building block **65** was developed by Barbas.[68,69] Application of O-*t*Bu-threonine as a catalyst in the cross-aldol reaction leads to the stereoselective formation of the 1,2-*syn* aldol product. This methodology was developed primarily for aromatic aldehydes.[70] However, our system requires the use of an aliphatic aldehyde. Building on previous experience with the proline-catalysed aldol reactions, 4-pentenal **84** was consequently chosen for investigation with O-*t*Bu-threonine. Ketone **65** was prepared by reacting dihydroxyacetone dimer **98** with an excess of TBSCl and imidazole to produce **65** in 95% yield (Scheme 2.4.1).



Scheme 2.4.1 Formation of the bis-TBS ketone 65.

With the starting materials in hand, investigation of the O-*t*Bu-threonine-catalysed aldol reaction began. The initial reaction was performed under conditions developed by Barbas, where ketone **65** was dissolved in *N*-methylpyrrolidone (NMP), and 4-pentenal **84** was added, followed by water and *O*-*t*Bu-threonine. The resulting mixture was stirred for three days (Table 2.4.1, entry 1). After work-up the crude mixture was analysed and traces

of the corresponding aldol product **99** were detected. Upon changing the solvent to dimethylformamide the aldol product **99** was formed in good selectivity, albeit in low yield (Table 2.4.1, entry 2). However, when the reaction was carried out in chloroform an acceptable, for the purpose of this study, 28% yield of **99** and good levels of diastereoselectivity (9 : 1) were obtained (Table 2.4.1, entry 3).

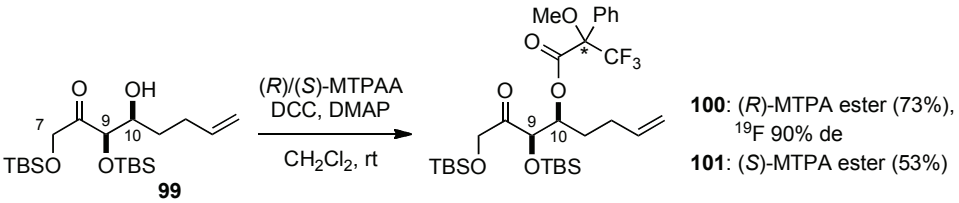


Entry	Conditions	Yield (%)	*syn* : *anti*
1	NMP, 3 vol% H_2O, 0 °C – rt, 3 days	traces	—
2	DMF, 3 vol% H_2O, 0 °C – rt, 3 days	19	9 : 1
3	$CHCl_3$, 3 vol% H_2O, 0 °C – rt, 5 days	28	9 : 1

Table 2.4.1 Synthesis of the aldol product 99 and optimisation of the reaction.

2.4.1 Determination of the absolute configuration at the C10 stereocentre

The absolute configuration of C10 stereocentre was confirmed by the preparation of the corresponding (*R*)- and (*S*)-MTPA esters **100** and **101**, and subsequent analysis by advanced Mosher method as described in section 2.2.1. Investigation of the ^{1}H NMR shifts of the Mosher ester **100** and **101** (Table 2.4.2) confirmed the expected (*S*)-configuration at the C10 hydroxyl-bearing centre. From the ^{19}F NMR (**Error! Reference source not found.**) enantiomeric excess of the major 9,10-*syn* diastereoisomers of **99** was calculated to be 90% *ee*.



Assignment	δ_s/ppm	δ_r/ppm	$\delta_s - \delta_r$/ppm
H-7a	4.49	4.35	0.14
H-7b	4.28	4.28	0.00
H-9	4.67	4.56	0.11
H-10	5.35	5.38	-0.03
H-13	5.69	5.77	-0.08
H-14	4.94	5.03	-0.09

Table 2.4.2 Synthesis of the (*R*)- and (*S*)-MTPA esters of β-hydroxy ketone 99 and ^{1}H NMR analysis.

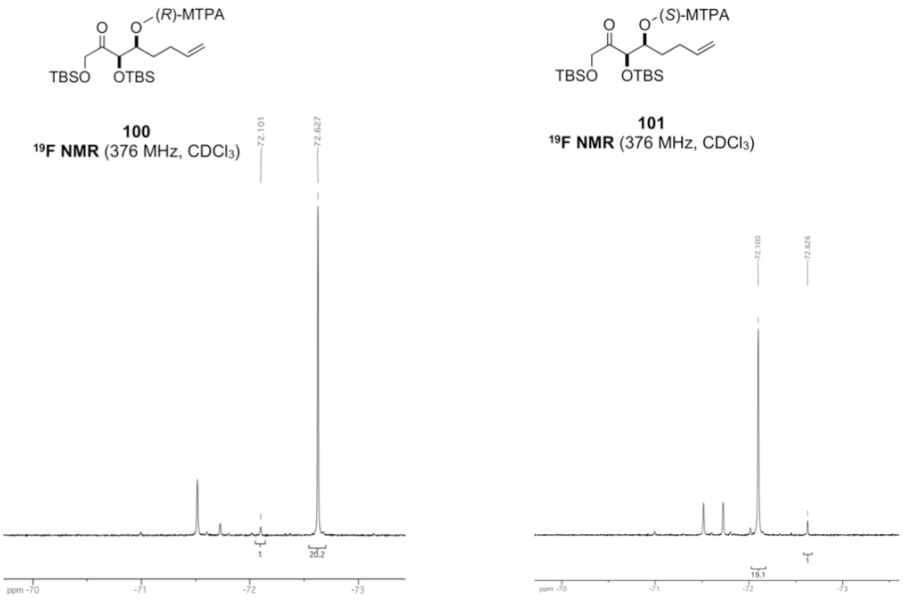


Figure 2.4.1 ^{19}F NMR of the (*R*)- and (*S*)-MTPA esters.

2.4.2 Mechanism of O-*t*Bu-threonine-catalysed aldol reaction

When O-*t*Bu-threonine is employed as a catalyst, the formation of a (*Z*)-enamine is preferred (Figure 2.4.2, **TS V**), which is dictated by hydrogen bonding between the amine hydrogen and oxygen of the alkoxy group. Facial selectivity of the approaching acceptor is controlled by the steric hindrance of the aldehyde and enamine substituents as well as proton transfer from the carboxylate onto the aldehyde oxygen (Figure 2.4.2, **TS VI**).[68]

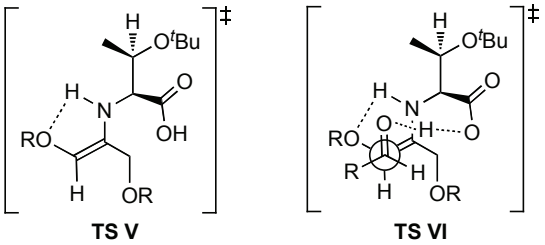
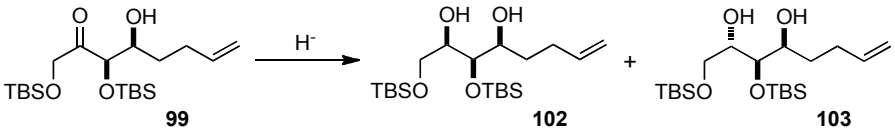


Figure 2.4.2 Barbas transition states for O-*t*Bu-threonine-catalysed aldol reaction.

2.4.3 Reduction of the 9,10-*syn* aldol product

With ample quantities of the 9,10-*syn* configured aldol product **99** in hand, the investigation of the 1,3-reduction commenced. Initial reduction with sodium borohydride gave 1,3-diol **102** in good yield (80%). However it was observed, that the silyl ether was labile under the reaction conditions returning a range of side products which were difficult to identify (Table 2.4.3, entry 1).

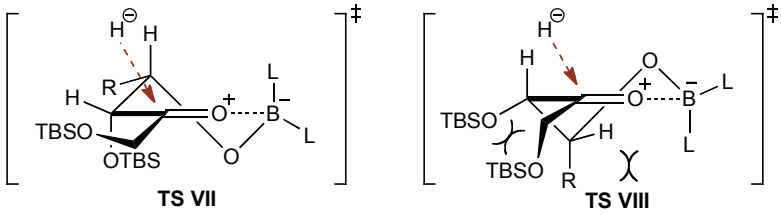


99 102 103

Entry	Conditions	Yield (%)	*syn* : *anti*
1	$NaBH_4$, MeOH, -78 ºC	80	*nd*
2	*i*) $cHex_2BCl•NEt_3$, $LiBH_3OMe$, THF, -78 ºC, *ii*) H_2O_2, MeOH, pH 7 buffer 0 ºC	84	10 : 1
3	$Me_4NBH(OAc)_3$, CH_3CN, AcOH, -78 to -30 ºC	—	—
4	$NaBH_4$, $CeCl_3•7H_2O$, MeOH, -78 ºC	61	10 : 1

Table 2.4.3 Studies of the reduction of β-hydroxy ketone 99.

Next, modification of the Narasaka-Prasad[71,72] protocol was investigated where β-hydroxyketone borinate chelate was reduced with $LiBH_3OMe$[73] (Table 2.4.3, entry 2). The reaction is believed to proceed *via* a chair-like transition state (Figure 2.4.3) in which a silyl substituent on the α-carbon prevents the approach of a reducing agent from the bottom side. Hence, hydride attacks preferentially from the *si*-face giving rise to the 1,3-*syn* diol **102** in excellent yield (84%) with good diastereoselectivity (10:1).

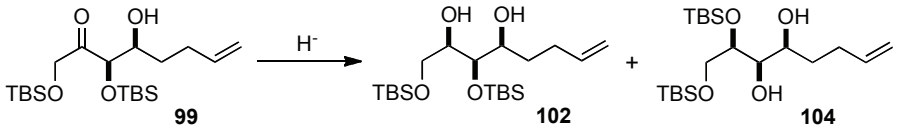


TS VII TS VIII

Figure 2.4.3 Proposed transition states for the reduction of the β-hydroxy ketone 99.

The 1,3-*anti* reduction of β-hydroxy ketone **99** was then required to access **103**. It was decided to apply the Evans protocol employing $Me_4NBH(OAc)_3$.[63] However, the acid-sensitive nature of compound **99** and the instability of the silyl groups in consequence led to degradation of the starting material (Table 2.4.3, entry 3).

The next possibility explored was the Luche reduction (Table 2.4.3, entry 4), which was a cleaner reaction compared to the one with sodium borohydride, and upon inspection of the ^1H NMR, the observed selectivity correlated to the results of reaction with $LiBH_3OMe$. At this point one of the side products, also observed in the reaction with sodium borohydride was isolated and analysed. It was assigned by COSY ^1H-^1H NMR to be compound **104** in which the secondary silyl group had migrated from the C9 position to the neighbouring C8 hydroxyl (Scheme 2.4.2). Faced with these results, it was necessary to search for an alternative plan to reach the 1,3-*anti* configured diol **103**.

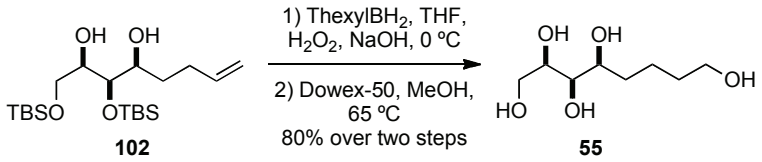


Scheme 2.4.2 Reduction of the β-hydroxy ketone 99.

Progress towards the degradation fragment **56** with the *anti-syn* arrangement and 8*S*, 9*R*, 10*S* configuration was now hampered, nonetheless the *syn-syn* 8*R*, 9*R*, 10*S* configured degradation fragment **55** was within reach.

2.4.4 Hydroboration and deprotection of the *syn* diol 102

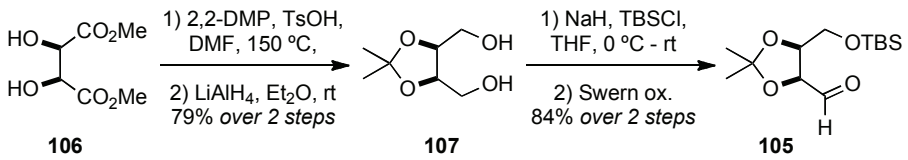
The hydroboration protocol employing thexylBH$_2$ successfully installed the C14 hydroxyl in **102**. However, it was observed by ^{1}H NMR that the silyl groups were displaced during the reaction. Therefore, Dowex-50 deprotection was instantly carried out to provide the *syn-syn* 8*R*, 9*R*, 10*S* configured degradation fragment **55** in excellent yield (80%) over two steps (Scheme 2.4.3).



Scheme 2.4.3 Formation of C8*R* C9*R* C10*S* degradation fragment 55.

2.5 *Meso*-tartaric acid route

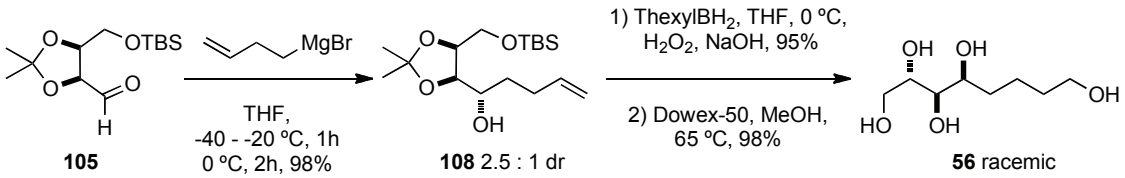
Due to the difficulties encountered in obtaining the 1,3-*anti* reduction product **103**, a synthesis starting from *meso*-tartaric acid was designed to access the fourth degradation fragment **56** as a racemate. Employing the protocols developed by Napoli *et al,*[74] aldehyde **105** was synthesised in four steps *via* a series of simple transformations in 66% yield (Scheme 2.5.1). The methyl ester of *meso*-tartaric acid **106** was first protected with dimethoxypropane and catalytic *p*-toluenesulfonic acid, followed by lithium-aluminium hydride reduction to afford diol **107**. Mono-TBS protection of **107** and oxidation under Swern conditions furnished aldehyde **105**.



106 **107** **105**

Scheme 2.5.1 Synthesis of the aldehyde 105 from *meso*-tartaric acid.

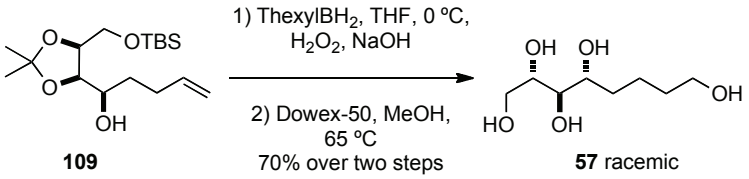
Addition of the freshly prepared homoallyl magnesium bromide to aldehyde **105** provided a separable mixture of C10-alcohols **108** and **109** (Scheme 2.5.2), which corresponded to the data reported by Napoli for saturated analogues. The isolated alcohol **108** was next subjected to hydroboration with thexylBH$_2$ to provide the intermediate diol, which was deprotected with Dowex-50 resin to furnish the racemic *anti-syn* degradation fragment **56**.



105 **108** 2.5 : 1 dr **56** racemic

Scheme 2.5.2 Formation of the racemic degradation fragment 56 *via* Grignard reaction.

The diastereomeric alcohol **109** was also subjected to hydroboration with thexylBH$_2$ and Dowex-50 deprotection to yield the racemic form of the previously reported *anti-anti* degradation fragment **57** (Scheme 2.5.3).



109 **57** racemic

Scheme 2.5.3 Synthesis of the racemic degradation fragment 57.

As a result, investigation based on the *meso*-tartaric acid route provided additional justification for the assignment of the relative configuration of the degradation fragments **56** and **57**. Assignment of the *anti-anti* racemic degradation fragment **57** obtained in this way was supported by the corresponding ^{1}H and ^{13}C NMR data of the enantiopure product **57** synthesised in 9,10-*anti* series. Consequently, product **56** derived from *(S)*-alcohol **108** would bear *anti-syn* configuration.

2.6 Structural assignment

At this stage, the first phase of the project was concluded with the synthesis of four diasteroisomeric C7-C14 polyols. The synthetic strategy employed highlights the effectiveness of organocatalysis for the construction of contiguous hydroxylated stereocentres from simple achiral building blocks. The collected ^{1}H and ^{13}C NMR and optical rotation data (Table 2.6.1) were sent to Prof. Bill Baker for comparison with the natural degradation fragment **54**. In due course we received confirmation of the relative and absolute stereochemistry of the C7-C14 fragment. Our collaborator identified the arrangement of the triad present in the macrocycle as the *syn-anti* 8*R*, 9*R*, 10*R* isomer, which was the enantiomer of the degradation fragment **58** (Figure 2.6.1). At this point, attention was directed towards the synthesis of the C7-C14 fragment with the proposed stereochemistry and its incorporation into the total synthesis of palmerolide C (**3a**).

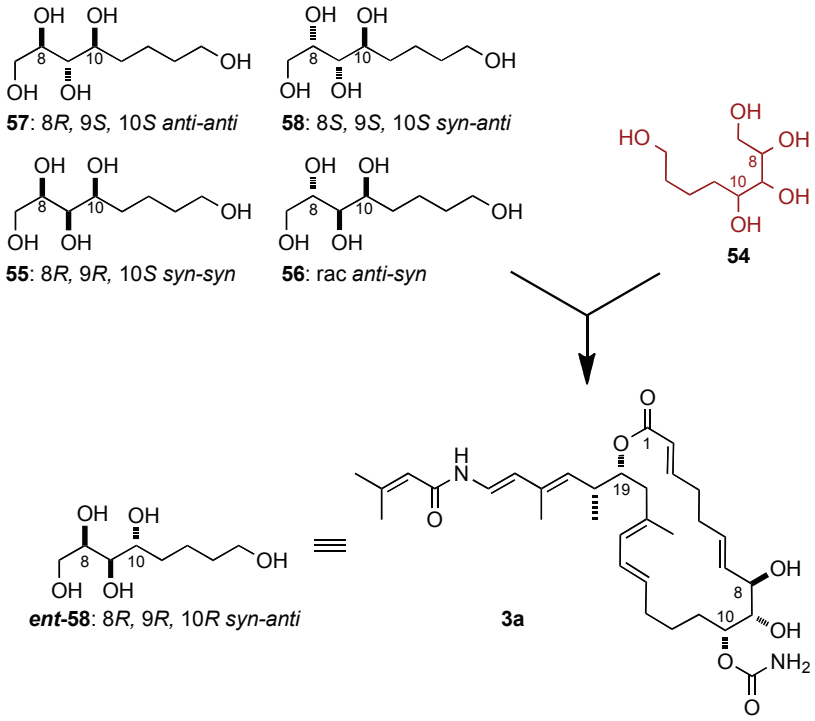
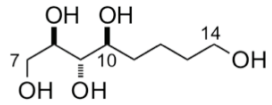
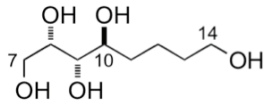
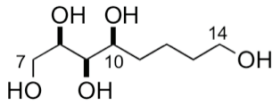
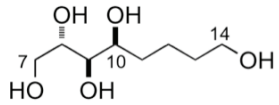


Figure 2.6.1 Comparison studies, performed by Prof Bill Baker, University of South Florida.

Table 2.6.1 Compilation of data for degradation fragment studies.

	 **57**: 8*R*, 9*S*, 10*S*		 **58**: 8*S*, 9*S*, 10*S*		 **55**: 8*R*, 9*R*, 10*S*		 **56**: 8*R*, 9*S*, 10*R*	
Proton No.	^{1}H, δ (m, *J* Hz)	^{13}C, δ	^{1}H, δ (m, *J* Hz)	^{13}C, δ	^{1}H, δ (m, *J* Hz)	^{13}C, δ	^{1}H, δ (m, *J* Hz)	^{13}C, δ
7A	3.77 (dd, 11.1, 3.2 Hz)	64.6	3.62-3.60 (m)	64.9	3.63 (dd, 12.1, 5.6 Hz)	64.4	3.79 (dd, 11.1, 3.5 Hz)	65.1
7B	3.61 (dd, 11.1, 6.2 Hz)						3.61 (dd, 11.1, 6.0 Hz)	
8	3.69-3.64 (m)	73.9	3.9 (td, 6.2, 2.0 Hz)	72.0	3.73-3.66 (m)	73.4	3.68 (ddd, 8.0, 5.9, 3.5 Hz)	71.4
9	3.47 (t, 6.4 Hz)	76.0	3.34 (dd, 6.5, 4.5 Hz)	74.8	3.44 (t, 4.0 Hz)	74.3	3.36 (dd, 10.9, 5.9 Hz)	74.5
10	3.69-3.64 (m)	74.5	3.65-3.60 (m)	72.6	3.73-3.66 (m)	74.0	3.82 (td, 4.3, 1.7 Hz)	73.2
11		33.7	A: 1.82-1.74 (m) B: 1.46-1.34 (m)	34.5		33.6		34.5
12	1.74-1.27 (m)	23.0	A: 1.64-1.50 (m) B: 1.46-1.34 (m)	23.0	1.63-1.41 (m)	23.1	1.65-1.48 (m)	23.4
13		33.0	1.64-1.50 (m)	33.7		34.2		33.7
14	3.57 (t, 6.5 Hz)	63.0	3.57 (t, 6.4 Hz)	63.0	3.57 (t, 6.4 Hz)	62.9	3.57 (t, 6.4 Hz)	62.9
$[\alpha]_D^{20}$	-8.6 (*c* 0.3, MeOH)		-2.6 (*c* 0.8, MeOH)		-2.0 (*c* 1.2, MeOH)		racemic, derived from *meso*-tartaric acid	
R_f	0.22 (10 % MeOH/CH_2Cl_2)							
HRMS	calcd. for $C_8H_{19}O_5$ $[M + H]^+$ 195.1227, found 195.1225		calcd. for $C_8H_{17}O_5$ $[M - H]^-$ 193.1081, found 193.1084		calcd. for $C_8H_{18}O_5$ $[M + Na]^+$ 217.1046, found 217.1047		calcd. for $C_8H_{19}O_5$ $[M + H]^+$ 195.1227, found 195.1227	

Chapter 3

3.1 Retrosynthetic strategy for the synthesis of C1-C14 fragment

The retrosynthetic strategy for the C1-C14 fragment **110** of palmerolide C is outlined in Figure 3.1.1. Based on the stereochemical information obtained from the degradation studies a highly convergent synthetic strategy was envisaged with disconnections of the C6-C7 alkene revealing two key fragments. The C1-C6 subunit **111**, could be derived from Horner-Wadsworth-Emmons reaction (HWE) of 4-pentenal **84** and triethyl phosphonoacetate **112**. The C7-C14 fragment **113** would be assembled *via* a boron aldol reaction between chiral ketone **114**, derived from the L-ascorbic acid and aldehyde **69**.

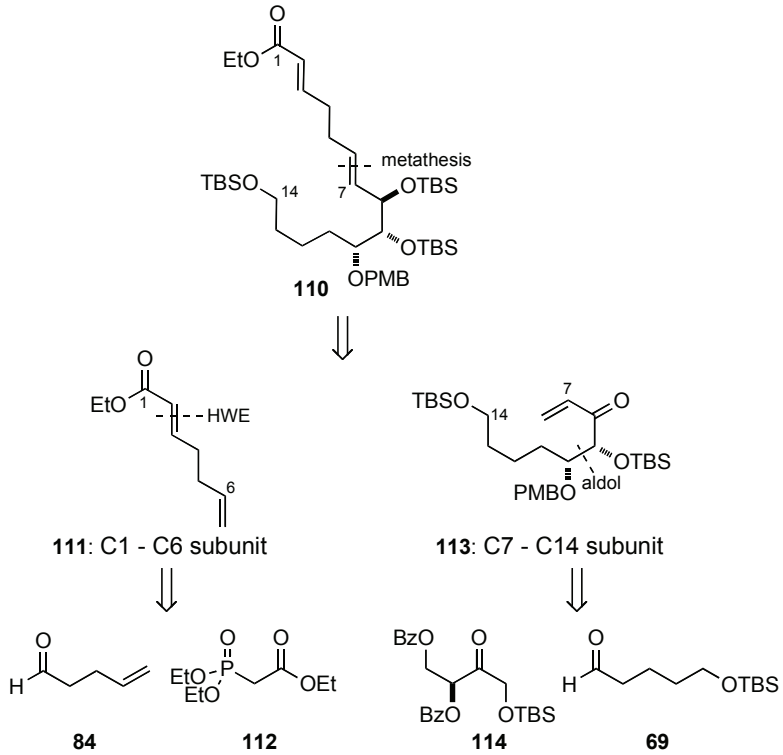
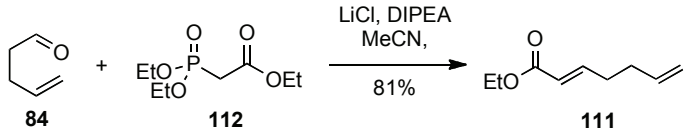


Figure 3.1.1 Retrosynthesis of the C1-C14 fragment 110.

3.2 Synthesis of the C1-C6 fragment 111

Preparation of the C1-C6 fragment **111** began with HWE olefination. Under Masamune-Roush conditions, treatment of 4-pentenal **84** with triethyl phosphonoacetate ester **112**, lithium chloride and Hunig's base, provided the *E*-enoate **111** exclusively in 81% yield (Scheme 3.2.1).[75]

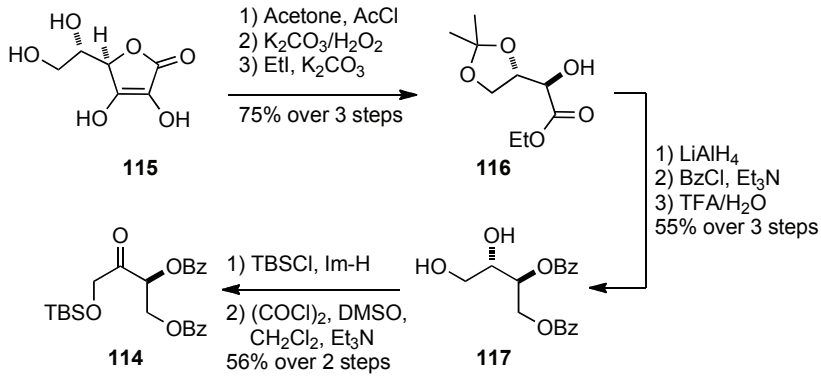


Scheme 3.2.1 Synthesis of the C1-C6 subunit 111 *via* HWE olefination.

3.3 Synthesis of the C7-C14 fragment

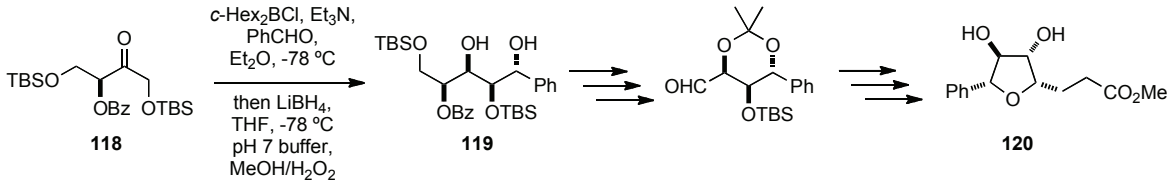
3.3.1 Synthesis of the chiral ketone

The construction of the key bond in the C7-C14 fragment relies on the boron-mediated aldol reaction of α-chiral ketone **114**.[76,77] The synthesis of **114** began with the introduction of the isopropylidene acetal on L-ascorbic acid **115** (Scheme 3.3.1). Oxidative cleavage of the resulting intermediate and subsequent esterification provided hydroxy-ester **116**. Reduction of the ester and protection of the resulting diol with benzoyl chloride was followed by the deprotection of the acetal, which provided **117**. Selective silyl protection of the primary hydroxyl and oxidation under Swern conditions provided access to the chiral ketone **114**. A total of eight steps from L-ascorbic acid was required to complete the synthesis of **114** in 23% overall yield.



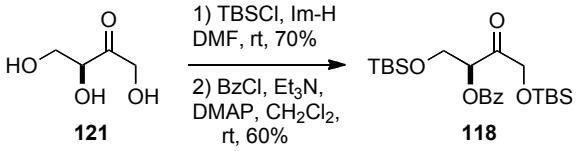
Scheme 3.3.1 Preparation of chiral ketone 114 from L-ascorbic acid.

Given the lengthy synthetic sequence required to prepare **114** which ultimately only provides two carbons, an alternative α-oxygenated chiral ketone was sought. Carda and Marco[78] demonstrated the potential of the L-erythrulose-derived ketone **118** in the formation of the poly-oxygenated chiral motifs of type **119**, which then were used in the synthesis of the bioactive metabolite (+)-goniothalesdiol **120** (Scheme 3.3.2).[78] Good levels of selectivity[79] and high yields of product **119** prompted exploration of the L-erythrulose derived ketone **118** in our approach towards C7-C14 subunit **113**.



Scheme 3.3.2 Synthesis of (+)-goniothalesdiol 120 from ketone 118.

Marco developed a two-step protocol utilising L-erythrulose **121** as a starting chiral ketone. The synthesis began with TBS-protection of the primary hydroxyl groups in **121**, further esterification of the secondary hydroxyl with benzoyl chloride completed **118** in good yield (Scheme 3.3.3).



Scheme 3.3.3 Preparation of the chiral ketone 118 from L-erythrulose.

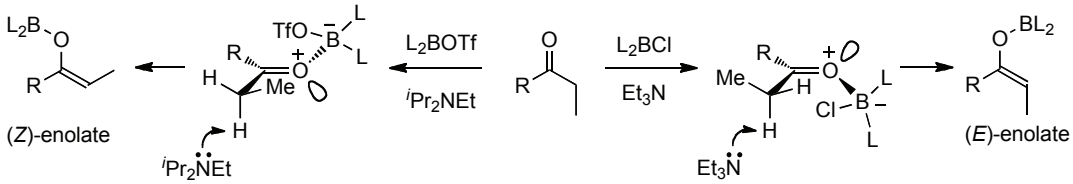
3.3.2 Boron-mediated aldol reaction

3.3.2.1 Stereocontrol in boron aldol reactions

The aldol motif is one of the most commonly occurring patterns within molecules derived from natural sources, particularly those of polyketide origin. The construction of the 1,3-hydroxy-ketone pattern presents chemists with a challenge that has been successfully tackled for over thirty years. As a result, examples of well-defined enolisation

protocols,[80] chiral auxiliaries,[81] and also ligands and catalysts[82] for use as stereochemical determinants have been developed.

One of the key factors in predicting the relative configuration of an aldol product (*syn* or *anti*) is the geometry of the enolate component; *syn*-aldol product being generated from (*Z*)-enolates, and *anti* products arising from (*E*)-enolates. Enolisation protocols using boron as a metal centre give access to defined enolate geometries, where under specific circumstances, factors such as electronic effects and steric effects govern the selectivity. The generation of the (*E*)-boron enolate under kinetic conditions can be achieved employing dicyclohexylboron chloride, which preferentially complexes the ketone C=O lone pair *cis* to the alkyl group allowing stabilisation of a negative charge (Me > Et > ^{i}Pr) (Scheme 3.3.4). As a result of this complexation, a proton on the activated centre can be abstracted by a relatively small amine base such as triethylamine, which consequently gives rise to the (*E*)-boron enolate. Kinetic conditions promoting the formation of the (*Z*)-enolate typically involves the use of small ligands (*e.g. n*-butyl) on boron and a good leaving group such as triflate, in combination with a bulky amine (*e.g.* diisopropylethylamine), leading to deprotonation of the most accessible proton which provides (*Z*)-enolate (Scheme 3.3.4).[80]



Scheme 3.3.4 Enolisation methods to form (*Z*)- and (*E*)-enolates.

When the (*Z*)-enolate reacts with the aldehyde, two Zimmerman-Traxler transition states **TS I** and **TS II** shown below can be considered (Figure 3.3.1). Due to 1,3-diaxial interactions between the boron-ligand (L), the enolate side chain (R^1) and the aldehyde substituents (R^3) transition state **TS II** is disfavoured, hence the preferred transition state **TS I**, which is lower in energy, would give rise to the 1,2-*syn* aldol product.

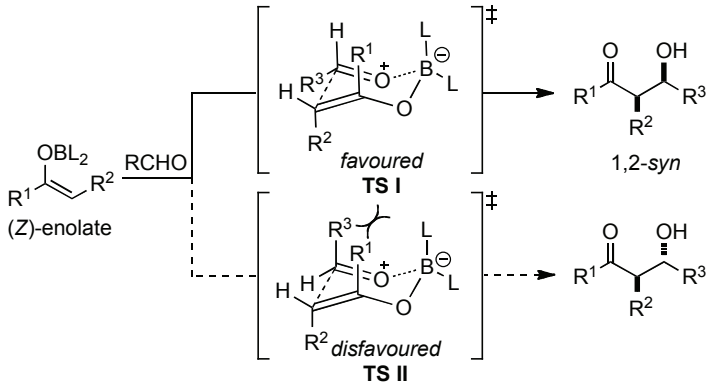


Figure 3.3.1 Zimmerman-Traxler transition states for (*Z*)-enolates.

Recent DFT calculations showed that boat-like transition states predominate when (*E*)-boron enolates are used in the aldol reaction (Figure 3.3.2). However, the relatively small energy barrier between **TS III** and **TS IV** lowers the level of enantiocontrol.[83] The steric interactions between the metal ligand and enolate side chain (R^1) are minimised in the aldol reaction proceeding *via* a boat-like transition state.

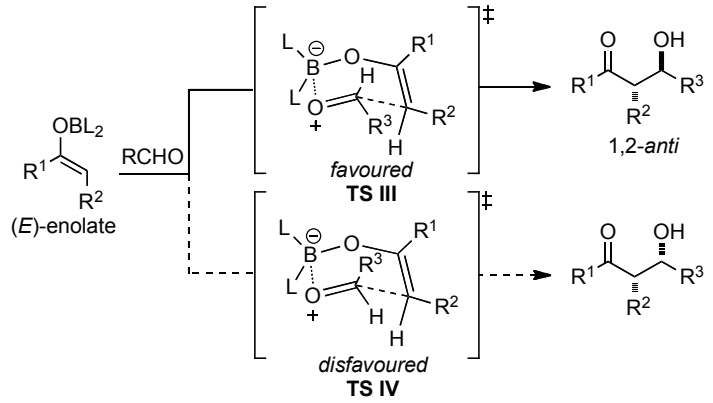
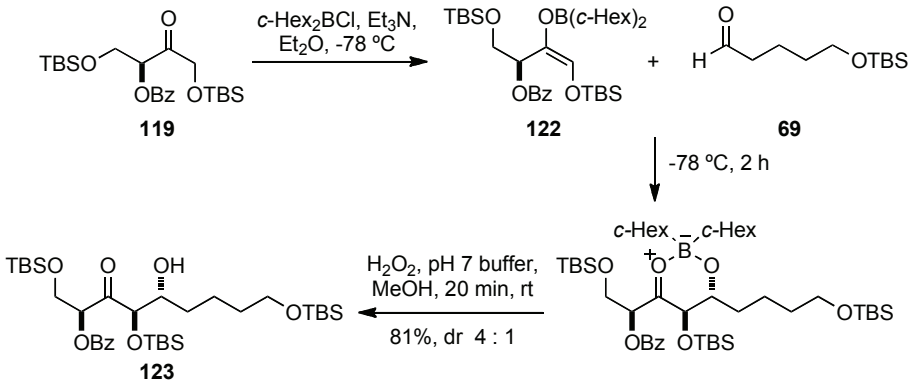


Figure 3.3.2 Boat-like transition states for (*E*)-enolates.

3.3.2.2 Boron-mediated aldol reaction using ketone 118

Investigation of the *anti*-selective aldol reaction using chiral ketone **118** and aldehyde **69**, commenced with the selective enolisation of **118** using *c*-Hex_2BCl and Et_3N to provide the intermediate (*E*)-boron enolate **122**. Followed by the addition of aldehyde **69** and oxidative work-up upon completion of the reaction, the corresponding aldol product **123** (Scheme 3.3.5) was delivered in good yield (81%) with moderate diastereoselectivity (4:1).



Scheme 3.3.5 Boron mediated *anti*-aldol reaction to form β-hydroxyketone 123.

The stereochemical outcome of the aldol reaction of chiral (*E*)-enol borinate **122** is determined by a number of competing effects. A plausible explanation for product distribution in the first instance depends upon enolate geometry and its π-facial selectivity. Favoured transition state **TS V** shown in Figure 3.3.3, corresponding to the enolate *re*-face attack on the aldehyde, would account for the preferred 7,9-*syn*-9,10-*anti* (natural product numbering) arrangement in the product **123**. The 1,3-allylic strain minimisation between α-carbon substituents and the enolate OTBS group overrides the non-reinforcing electronic effect of the enol oxygen and α-benzoyl oxygen. The benzoyl substituent is directed in contrasteric fashion, nonetheless stabilising transition state **TS V** by hydrogen-bonding to the formyl hydrogen (Figure 3.3.3).[79,84] To restrain the steric hindrance between the α-OBz moiety and one of the boron cyclohexyl ligands, the boat-like transition state **TS V** would predominate over a chair-like transition state.[85]

The product **124** corresponding to the enolate *si*-face attack on the aldehyde, would be formed as a consequence of a much less stable transition state **TS VI**. The α-OBz substituent is now located away from the pseudo-cycle, pushing the sterically more demanding OTBS group inwards, however this interaction can be relieved through the rotation of the B—O bonds resulting in a boat-like conformation **TS VI**, though lacking the formyl hydrogen-bond stabilisation.

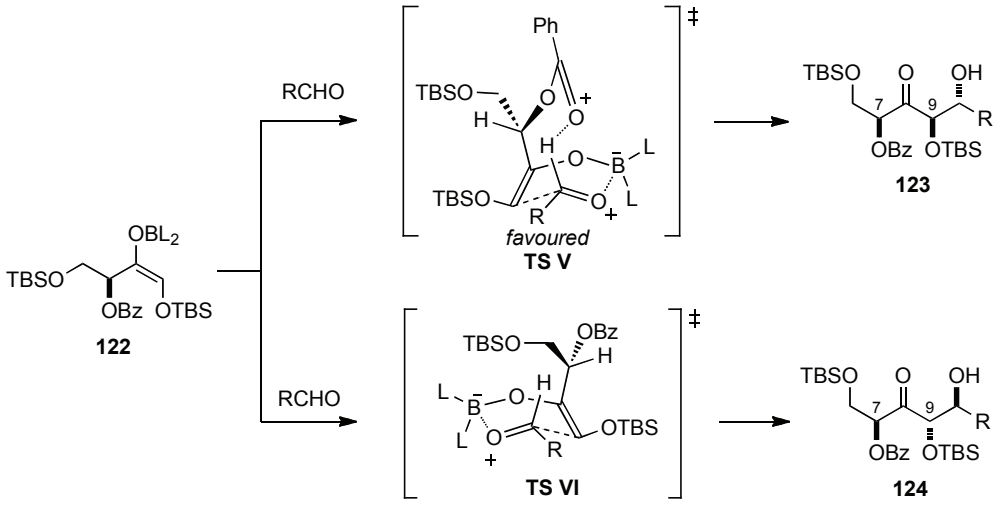
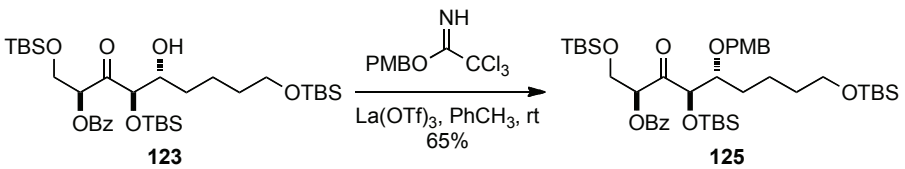


Figure 3.3.3 Rational for observed diastereoselectivity in boron-aldol reaction of chiral (*E*)-borinate 122.

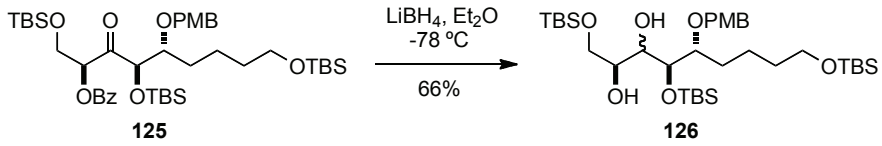
3.3.2.3 Completion of the synthesis of C7-C14 fragment

Having formed the aldol product **123**, it was observed that it is prone to rapid decomposition. Therefore, immediate protection of the C10 hydroxyl was required. However, the introduction of most protecting groups requires strong base or acid to effectively induce the desired transformation. In 2003, Basu and Rai reported a mild procedure to protect a hydroxyl group as its *p*-methoxybenzyl ether.[86] The protocol employs trichloroacetimidate of *p*-methoxybenzyl alcohol and a catalytic amount of mild Lewis acids, such as $La(OTf)_3$ or $Sc(OTf)_3$ to efficiently form benzyl ethers with primary and secondary alcohols. With the awareness that this procedure has been widely employed in the synthesis of complex molecules,[87,88] it was attempted first. Aldol product **123** was treated with PMBTCA and $La(OTf)_3$ (Scheme 3.3.6), and the reaction was completed after six hours. Filtration, followed by column chromatography provided **125** in 65% yield.



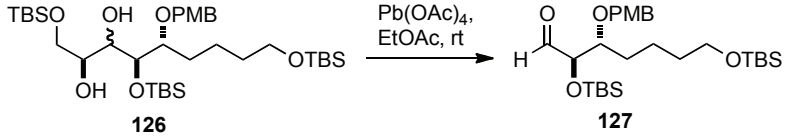
Scheme 3.3.6 Introduction of the PMB group to form 125.

Reduction of keto-ester **125** using lithium-aluminium hydride provided poor results, however using lithium borohydride a mixture of diols **126** was produced in 66% yield. Separation of the diastereoisomers at this point was not required as in the next step the newly formed stereocentre would undergo oxidative cleavage to form the aldehyde **127**.



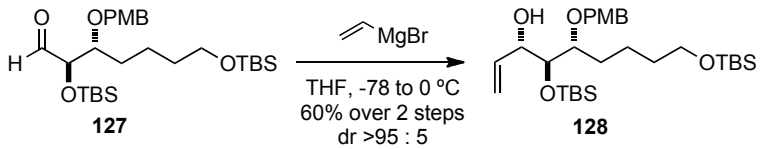
Scheme 3.3.7 Formation of diol 126.

Oxidative cleavage of 1,2-diol **126** with sodium *meta*-periodate was explored initially, however unsatisfactory results were obtained. Alternative cleavage with lead tetracetate provided the α,β-bisalkoxy aldehyde **127** almost quantitatively (Scheme 3.3.8). Quick filtration and removal of solvent gave access to crude **127**, which was used without further purification in the next step.



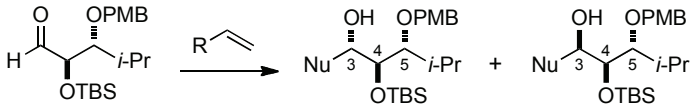
Scheme 3.3.8 Synthesis of aldehyde 127.

The synthesis of C7-C14 allylic alcohol **128** was completed with Grignard addition of vinyl magnesium bromide to the aldehyde **127** (Scheme 3.3.9). The allylic alcohol **128** was formed in 60% yield over two steps and with excellent >95 : 5 diastereoselectivity.



Scheme 3.3.9 Formation of C7-C14 allylic alcohol 128

In 2006 Evans and co-workers investigated the asymmetric induction in methyl ketone aldol additions to α,β-bisalkoxy aldehydes and based on the experimental data, reported that the selectivity in acyclic substrates can be predicted upon consideration of the polar Felkin-Anh or Cornforth models.[89] In the reactions of 4,5-*anti*-bis-alkoxy aldehyde **129** preference for the formation of 3,4-*anti* products **130** rather than **131** was observed (Table 3.3.1), resulting from a π-facial selectivity of the aldehyde, antiparallel arrangement between the C=O and α-C-O groups, and minimisation of the *syn*-pentane interactions. Extrapolating these results to our system, the proposed transition state **TS VII** (Figure 3.3.4) derived from a minimisation of the *syn*-pentane interactions, accounts for the observed selectivity in the 8,9-*anti* allylic alcohol **128**.



129 **130** **131**

	3,4-*anti* : 3,4-*syn* (yield %)		
R	M = TMS/BF_3•OEt_2	M = 9-BBN	M = Li
Me	65 : 35 (83)	91 : 09 (88)	> 99 : 01 (95)
i-Pr	41 : 59 (95)	86 : 14 (92)	> 99 : 01 (95)
t-Bu	09 : 91 (89)	81 : 19 (90)	> 99 : 01 (98)

Table 3.3.1 Aldol addition to α,β-bisalkoxy aldehyde 129

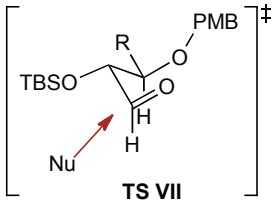


Figure 3.3.4 Evans-Cornforth model for addition to α,β-bisalkoxy aldehyde.

Comparison with similar allylic alcohols **132** and **133** studied by Pikho during the synthesis of pectenotoxin-2[90] supported our stereochemical assignment. The reported *J*-coupling values for 3,4-*syn* arrangement in the allylic alcohol **133** are around 2.0 Hz and in the 3,4-*anti* configured product **132** over 6.0 Hz (Figure 3.3.5). Inspection of the ^{1}H NMR spectra of **128** provided results consistent with 8,9-*anti* configuration where $J_{H8\text{-}H9}$ was 5.0 Hz.

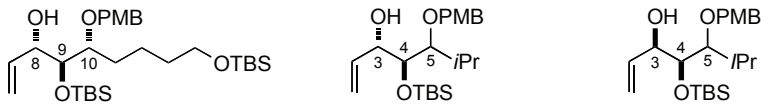
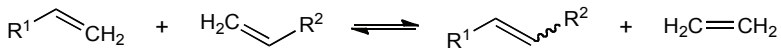


Figure 3.3.5 Comparison of the *J* values for 1,2-*syn* and 1,2-*anti* arrangement.

After completing the analysis of the obtained data it became apparent that the allylic alcohol **128** possessed the undesired *(S)* stereochemistry at the newly formed C8 stereocentre. Nevertheless, it was decided to explore the feasibility of a coupling strategy between C1-C6 subunit **111** and C7-C14 fragment **128**, while revising the synthetic strategy to install the correct configuration at C8 in allylic alcohol **128**.

3.4 Installation of the C6-C7 junction *via* cross-metathesis

Synthetic efforts turned towards the investigation of cross-metathesis (CM) between the C1-C6 **111** and C7-C14 **128** fragments. According to the definition, olefin metathesis is a unique metal-catalysed carbon skeleton redistribution in which a mutual exchange of unsaturated carbon-carbon bonds takes place.[91] CM is one variant of that transformation, where two different olefins are cleaved, aided by a catalyst, and recombined in such a way to form the new alkene and liberate ethene. This process is subjected to the thermodynamic rules (Scheme 3.4.1) in which case the external delivery of ethene would reverse the reaction.



Scheme 3.4.1 Cross-metathesis reaction.

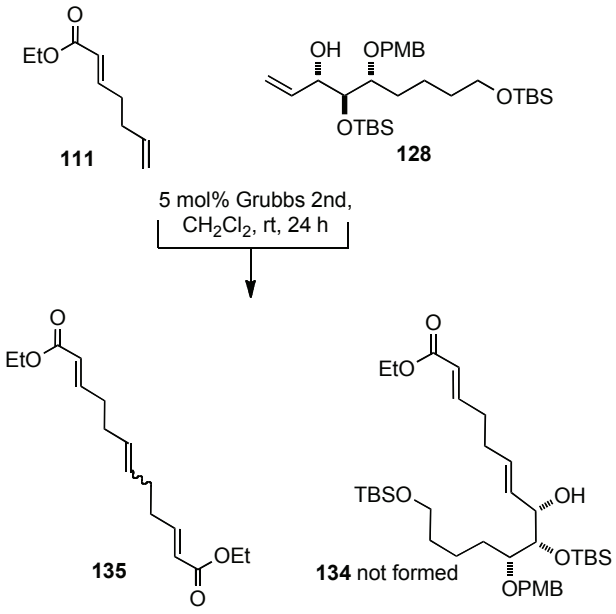
Despite broad interest and vast synthetic applications, the CM reaction presents certain limitations, with alkene selectivity being the major issue. In addition, complex product mixtures containing homodimers, heterodimers and side products are often obtained (complicating the purification and resulting in low yields).

To systematise the utility of the particular olefins in the process, categorisation and rules for selective CM have been established (Figure 3.4.1) after thorough investigation of literature examples.[91]

Olefin reactivity ↑	Type I	Rapid homodimerisation, homodimers consumable, *i.e.* terminal olefins, 1º allylic alcohols, esters.
	Type II	Slow homodimerisation, homodimers hardly consumable, *i.e.* styrenes, acrylates, acrylamides, 2º allylic alcohols.
	Type III	No homodimerisation, *i.e.* 1,1-disubstituted olefins, 3º allylic alcohols.
	Type IV	Olefins inert to CM, but do not deactivate catalyst (spectator), *i.e.* vinyl nitro olefins, trisubstituted allyl alcohols (protected).
Product distribution	Reaction between two olefins of Type I = Statistical CM.	
	Reaction between two olefins of same type (Type II or III) = Non-selective CM.	
	Reaction between olefins of two different types = Potentially selective CM.	

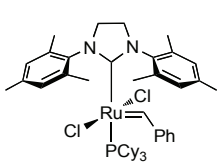
Figure 3.4.1 Olefin categories according to Grubbs.[91]

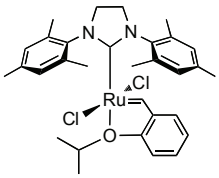
The investigation of our system began with the exploration of the second generation of the Grubbs catalyst[92] under the standard conditions for CM (5 mol% cat., CH_2Cl_2, rt, Scheme 3.4.2). In the tentative experiment determination of **111** and **128** olefin categories was addressed and general information about the performance of this system were acquired.

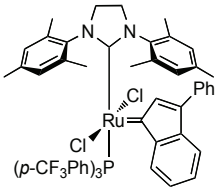


Scheme 3.4.2 Attempted cross-metathesis between C1-C6 and C7-C14 subunits.

Unfortunately, under the investigated conditions formation of the heterodimer **134** was not observed, only the homodimer of the C1-C6 fragment **135** was isolated in 30% yield together with unreacted **128** (40%). Upon evaluation of this experiment it was hypothesised that the C1-C6 fragment **111** behaves like a Type I olefin whereas the allylic alcohol **128**, despite being inactive in the cross metathesis, was involved in undetermined side reactions and so its classification remains ambiguous. The complex ^{1}H NMR spectra and unequal mass balance for compound **128** after the reaction suggested it was decomposing under the reaction conditions. Guided by these findings, considerable efforts were expended to achieve the cross coupled product, whilst employing different reaction conditions, which are summarised in Table 3.4.1. However, none of the catalysts screened in the different combinations of reaction parameters delivered the heterodimeric product **134**, promoting, at best the formation of the homodimer **135**.







Catalyst	Grubbs 2nd	Grubbs-Hoveyda	Nolan-type
Cat. loading	5-50 mol% cat	10 mol% cat	5-50 mol% cat
Concen.	0.001-0.1 M/CH_2Cl_2	0.001 M/CH_2Cl_2	0.001-0.1 M/CH_2Cl_2
Time	12 - 48 h at rt	24 h at rt	12 - 48 h at rt
111:**128** (eq)	1 to 10 : 1 to 2	5 : 1	1 to 10 : 1 to 2
Result	dimer **135** (30%), unreacted **128** (40%)	dimer **135** (25%), complex mix	

Table 3.4.1 Investigation of different conditions for CM reaction.

3.5 C7-C14 fragment - structural reassignment

While revising the C7-C14 synthesis and seeking an alternative coupling strategy further information pertaining to the stereochemistry of palmerolide C was provided. The initial assignment of the C8-C10 stereotriad was incorrect and revised to *syn-anti* 8*S*, 9*S*, 10*S*, while the 19*R*, 20*S* were the same (Figure 3.5.1). This was due to an error in the Mosher ester analysis arising from the use of MTPA-acid chlorides where, according to Cahn-Ingold-Prelog rules, *(R)*-MTPA acid gives the *(R)*-ester but *(R)*-MTPA acid chloride

provides the (*S*)-ester. The spectra for the (*R*)- and (*S*)-esters were transposed resulting in the opposite assignment (Section 2.6, Chapter 2).

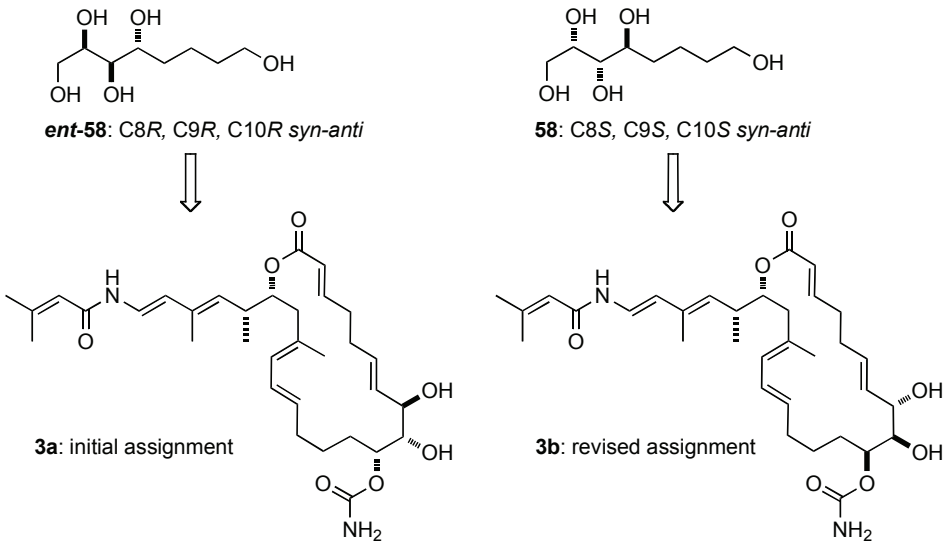
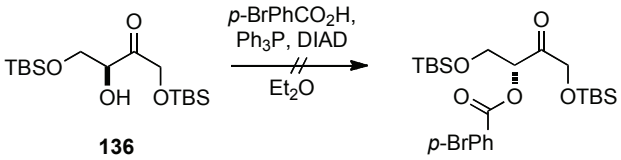


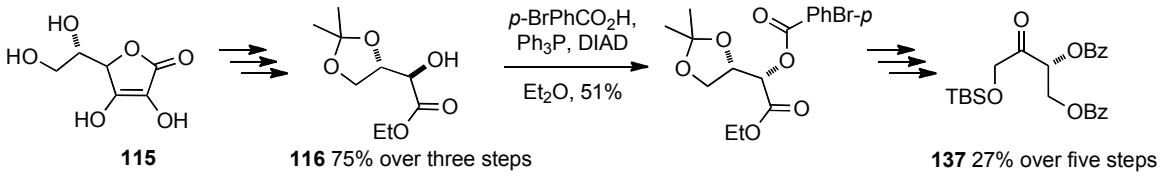
Figure 3.5.1 Revision of the configuration of palmerolide C.

In light of this revision, a synthesis reflecting the new assignment had to be devised. The immediate solution would be to change the configuration of the chiral ketone **119** to allow formation of the opposite enantiomer of the aldol product **123**. However, D-erythrulose at the cost of $ 700 USD for 100 mg was not seen as viable. Attempts to invert the stereocentre in the TBS-protected L-erythrulose **136** using a Mitsunobu reaction were unsuccessful (Scheme 3.5.1).



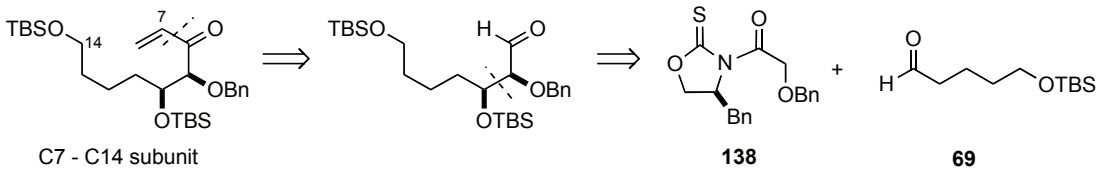
Scheme 3.5.1 Attempted Mitsunobu reaction to form D-erythrulose derivative.

The only possibility left within the approach of changing the stereochemistry on the chiral ketone **114** was to elaborate the route starting from L-ascorbic acid **115**. This unfortunately resulted in a nine-step synthesis for one of the starting materials **137** which was produced in 10% overall yield (Scheme 3.5.2).



Scheme 3.5.2 Synthesis of the *(R)*-configured ketone 137.

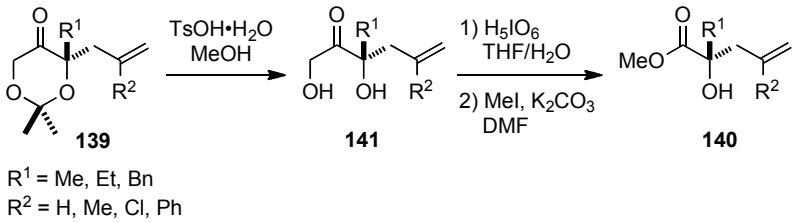
Undaunted, alternatives were sought and soon a revised plan was developed wherein the Crimmins[93] thioxazoline **138** was employed in the aldol transformation to control the installation of the required stereocentres (Scheme 3.5.3). A revised strategy would considerably reduce the number of synthetic operations towards C7-C14 fragment, with the *N*-glycolyloxazolidinethione auxiliary **138** prepared in three steps from *(S)*-phenylalanine.



Scheme 3.5.3 Revised retrosynthesis of the C7-C14 fragment.

3.6 Revised synthetic strategy for the C1-C14 fragment

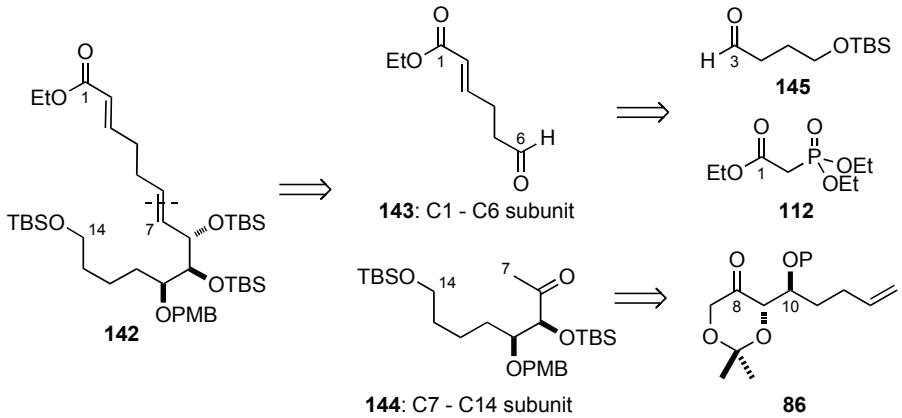
Several steps into our new synthetic approach towards Crimmins' thioauxiliary it was realised that the commercial supply of sparteine, a key component in this aldol reaction, was no longer available. Since our reserve of sparteine were quite limited, revision of the proposed strategy was inevitable. Gratifyingly, it was found that the aldol product **86** synthesised previously could be converted to α-hydroxy ester using a reaction developed by Stoltz.[94] This study showed application of dioxanone-derived products in a stereoselective alkylation reaction and further elaboration of the product **139** to the corresponding α-hydroxyesters **140** as shown in Scheme 3.6.1.



Scheme 3.6.1 Formation of the α-hydroxy-ester 140 by Stoltz.

One drawback of this approach would be regioselectivity for oxidative cleavage in the absence of a quaternary α-centre as in **141** (Scheme 3.6.1). However, only a synthetic investigation could provide valuable information. Therefore, it was decided to explore the acetonide deprotection, periodic acid-mediated cleavage and esterification on the suitably protected aldol product **86**.

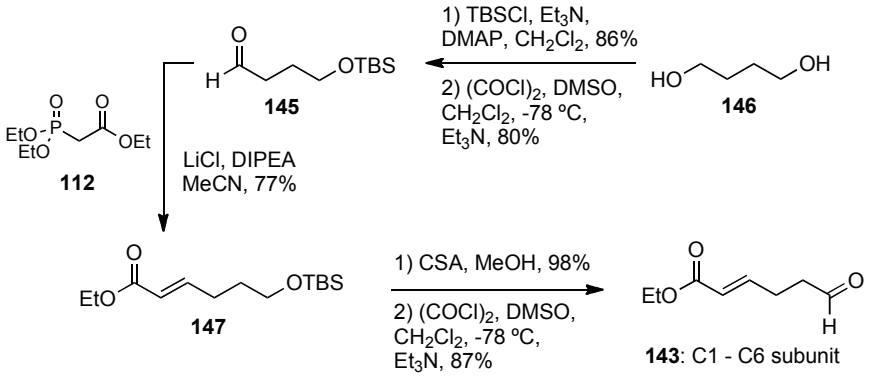
Bearing in mind the unsuccessful cross-metathesis studies, different coupling strategies were sought. As outlined in Scheme 3.6.2, the revised strategy towards **142** would rely on a C6-C7 aldol/dehydration disconnection revealing C1-C6 aldehyde **143** and C7-C14 ketone **144**. The synthesis of ketone **144** with C9-C10 stereocentres installed by the proline-catalysed aldol reaction would incorporate the acetonide deprotection and oxidative cleavage to form carboxylic acid. The modified C1-C6 subunit **143** would be accessed using a HWE reaction of aldehyde **145** and triethyl phosphonoacetate **112**.



Scheme 3.6.2 Retrosynthesis of the C1-C14 fragment 142.

3.3.2 Synthesis of the modified C1-C6 fragment

The construction of the C1-C6 subunit **143** began with the preparation of the aldehyde **145**. 1,4-Butanediol **146** was monoprotected with TBSCl, subsequent oxidation under Swern conditions delivered **145** in 68% over two steps (Scheme 3.6.3). HWE olefination of the aldehyde **145** with triethyl phosphonoacetate **112** was performed under Masamune-Roush conditions.[75] The enoate **147** was produced in 77% yield as a single *(E)*-isomer (Scheme 3.6.3). Following TBS-ether cleavage, Swern oxidation completed the synthesis of C1-C6 fragment **143**[95] in overall 41% yield over five steps.

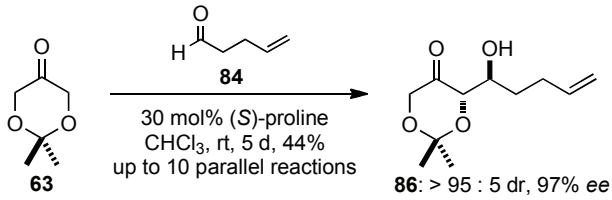


Scheme 3.6.3 Synthesis of the modified C1-C6 subunit 143.

3.3.3 Synthesis of the modified C7-C14 fragment

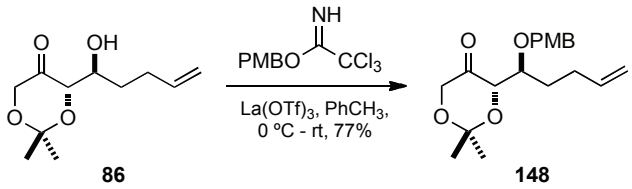
Attention was then turned to the synthesis of the aldol product **86** under proline-catalysis. The work commenced with the preparation of bulk quantities of the starting materials applying the same methods as for the small-scale synthesis. The aldehyde **84** was readily accessed in more than 20 g scale. Synthesis of dioxanone **63** on >50 g scale was more laborious; the initial acetonide **71** formation was carried out in DMF (Section 2.2), following a long extraction process producing high volume of solvents, which have to be removed. Removal of all traces of DMF before periodate cleavage was essential, as its similar boiling point with the final product made distillation troublesome. Consequently, dioxanone **63** was produced in >30 g quantity after distillation. The proline-catalysed reaction was then attempted on >10 g (76.9 mmol) of ketone **63** and surprisingly the cross-aldol product was produced in very low yield together with a range of side products making the column chromatography purification difficult. Therefore, several reactions (5-10) in parallel on a gram scale of ketone **63** were carried out and gratifyingly, **86** was

isolated typically in 40-50% yield per batch (Scheme 3.6.4).



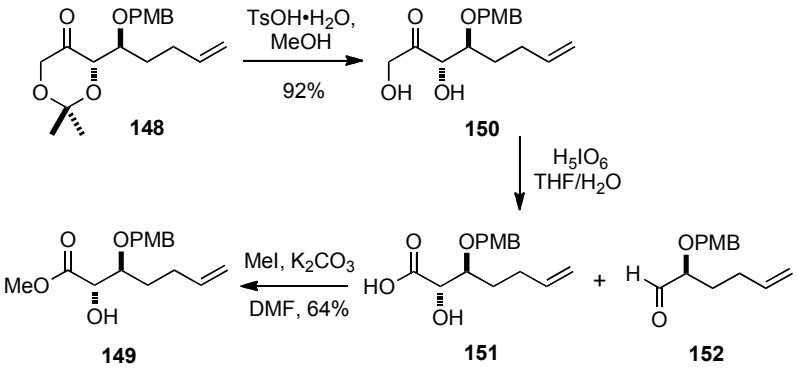
Scheme 3.6.4 Synthesis of the protected (*S*)-proline aldol product 86.

Following the isolation of **86**, installation of the protecting group required application of a mild protocol (Scheme 3.6.5). Therefore, *p*-methoxybenzyl trichloroacetimidate was employed in combination with catalytic lanthanide triflate to form C10 PMB-ether **148** in 77% yield.



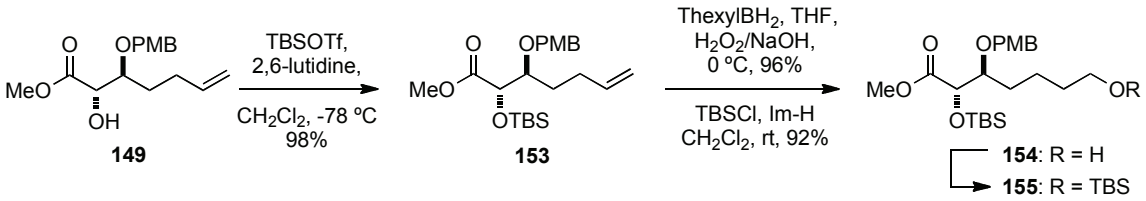
Scheme 3.6.5 Introduction of the PMB group to form 148.

With **148** in hand, attention turned towards formation of the α-hydroxy ester **149**. The acetonide **148** was subjected to deprotection with *p*-toluenesulfonic acid to access keto-diol **150** in 92% yield (Scheme 3.6.6). Subsequent periodic acid oxidative cleavage afforded the intermediate α-hydroxy carboxylic acid **151** together with aldehyde **152**, which were taken as a crude mixture for alkylation with methyl iodide. Upon completion of the reaction, column chromatography afforded α-hydroxy ester **149** in 64% yield and aldehyde **152** in 31%.



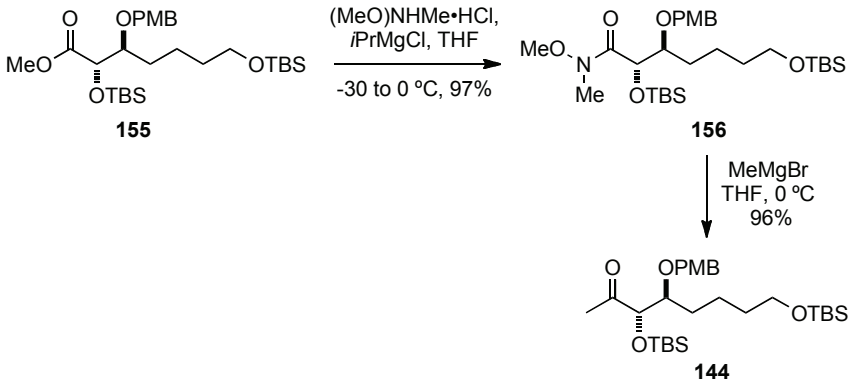
Scheme 3.6.6 Formation of the α-hydroxy ester 149.

With α-hydroxy ester **149** in hand, protection with TBSOTf and 2,6-lutidine gave **153** in 98% yield (Scheme 3.6.7). Installation of a terminal hydroxyl functionality was then required, and having previously used thexylBH$_2$ we decided to explore the optimised conditions. Therefore, compound **153** was added to a freshly prepared solution of thexylBH$_2$ in tetrahydrofuran to furnish alcohol **154** after oxidative work-up in excellent 96% yield (Scheme 3.6.7). Subsequent protection using TBSCl and imidazole afforded the intermediate **155** in 92% yield.



Scheme 3.6.7 Synthetic elaboration of α-hydroxy ester 149.

Having prepared compound **155**, all that remained was to form methyl ketone **144** (Scheme 3.6.8). We chose to first introduce a Weinreb amide functionality to allow controlled alkylation with methyl Grignard. To ester **155** and *N,O*-dimethylhydroxylamine hydrochloride was added isopropylmagnesium bromide and intermediate Weinreb amide[96] **156** was isolated in 97% yield. Subsequent addition of methylmagnesium bromide afforded methyl ketone **144** in 96% yield.



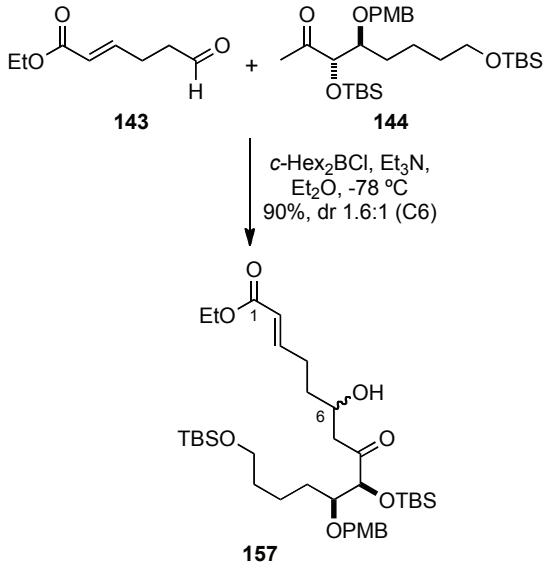
Scheme 3.6.8 Completion of the synthesis of the C7-C14 subunit 144.

The C7-C14 methyl ketone **144** was synthesised in nine steps including the proline-catalysed aldol reaction, which installed the desired stereochemistry with an excellent diastereo- and enantiocontrol. However, the isolated yield of the aldol product **86** is the

only disadvantageous feature of this organocatalytic approach. Nonetheless, the remaining synthetic operations produced C7-C14 subunit **144** in 36% yield over eight steps.

3.7 Revised fragment union

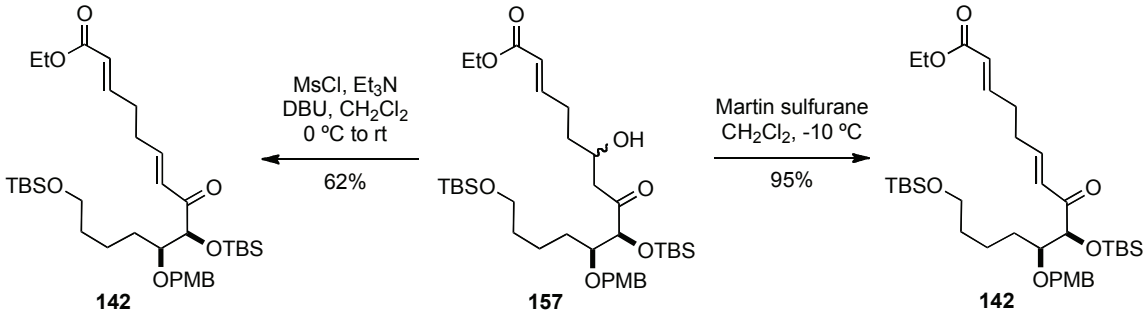
Having synthesised C1-C6 **143** and C7-C14 **144** fragments, attention was turned towards their coupling using an aldol/dehydration sequence. Building upon previous experience it was decided to utilise the boron aldol reaction to unite the two carbonyl components.[97] Selectivity was not an issue, since elimination of the newly formed stereocentre would immediately follows the C—C bond forming step. Thus, enolisation of C7-C14 ketone **144** with *c*-Hex_2BCl and triethylamine in diethyl ether at -78 ºC, followed by addition of aldehyde **143**, provided the corresponding aldol adducts **157** as an inconsequential mixture of C6 diastereoisomers (90%, 1.6 : 1 dr, Scheme 3.7.1)



Scheme 3.7.1 C1-C6 and C7-C14 fragment union *via* aldol coupling.

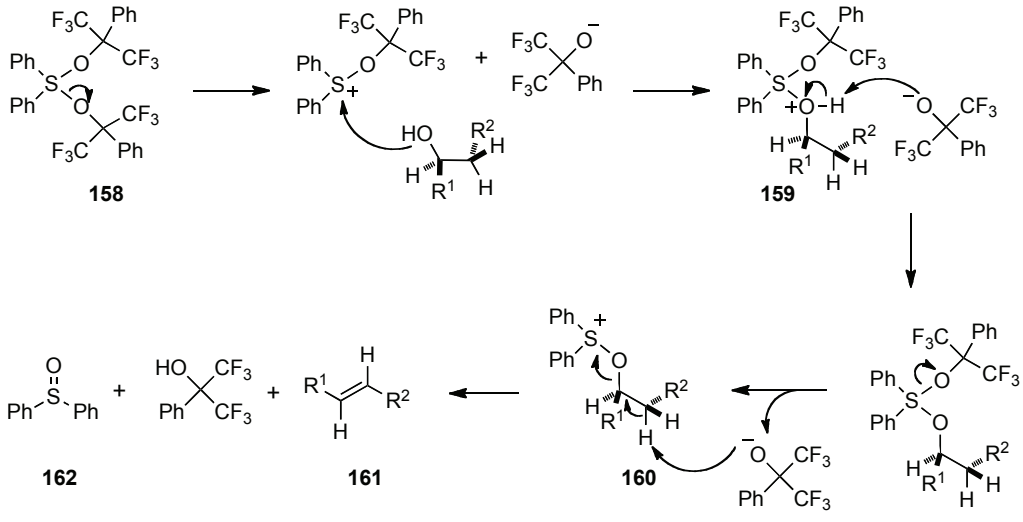
Next, the one-pot mesylation/elimination procedure[98] was explored. Even though it provided desired product **142**, the obtained yield was unsatisfactory and extended exposure to DBU did not show any improvement in yield (Scheme 3.7.2). An alternative method utilising dehydrating agents such as the Burgess or Martin sulfurane reagents were considered next. Both procedures are reported to efficiently eliminate a molecule of water from secondary and tertiary alcohols. The first reagent methyl *N*-(triethyl-ammoniumsulfonyl)carbamate (Burgess reagent), was found to proceed through E1

elimination pathway, abstracting hydrogen in *syn* relation to the leaving group due to the geometrical constraints on the reagent.[99] Inspection of the literature showed Martin sulfurane reacts with secondary alcohols *via* E2 elimination. The antiperiplanar geometry in this step enables stereospecific alkene generation from chiral secondary alcohols. Hence, we chose to investigate dehydration with Martin sulfurane reagent. Treatment of **157** with a solution of the Martin sulfurane[100] reagent at -10 ºC provided enone **142** in less than one hour in excellent 95% yield and exclusive *(E)*-selectivity.



Scheme 3.7.2 Dehydration of the aldol product 157 to form enone 142.

Martin sulfurane reagent **158** (Scheme 3.7.3), is a ketal analogue of bi-phenylsulfide, which reacts by rapid exchange of one of the alkoxy ligands with the reacting alcohol to yield sulfurane **159** and fluoro-alcohol. Key intermediate alkoxysulfonium ion **160** is formed upon extrusion of the other fluoro-alkoxy ligand, which comes back to attack the α-hydrogen and release alkene **161** and bi-phenyl sulfoxide **162** (Scheme 3.7.3).

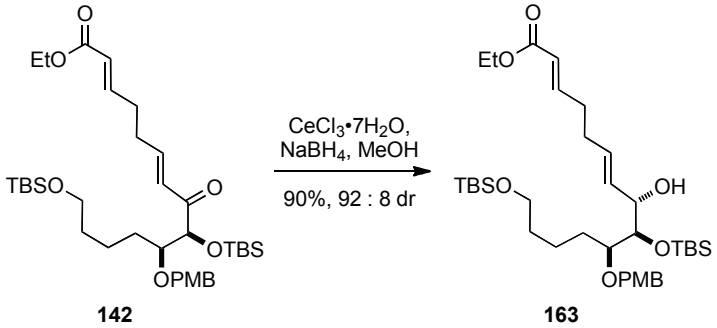


Scheme 3.7.3 Proposed mechanism of Martin sulfurane dehydration.

3.8 Advancing the C1-C14 subunit

3.8.1 Reduction of enone 142 and configurational analysis

With the C1-C14 fragment **142** in hand, investigation of the enone reduction began. Drawing upon previous experience with addition to α,β-bisalkoxyaldehyde **127** high levels of control in the reduction of **142** were expected (see section 3.3.2.3). The selective conversion of enone **142** to the allylic alcohol **163** was achieved under Luche conditions employing cerium chloride and sodium borohydride. The reduction product **163** was formed in excellent 90% yield and 92 : 8 diastereoselectivity, as established by ^{1}H NMR (Scheme 3.8.1).



Scheme 3.8.1 Reduction of enone 142 introducing C8 stereocentre.

The diastereoselection can be explained by consideration of the Evans-Cornforth model discussed in section 3.3.2.3.[89] However, in this instance direct minimisation of the *syn*-pentane interactions (**TS VIII**) promotes formation of the C8*S* configured product **163** (Figure 3.8.1).

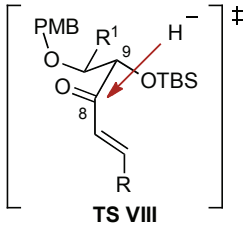
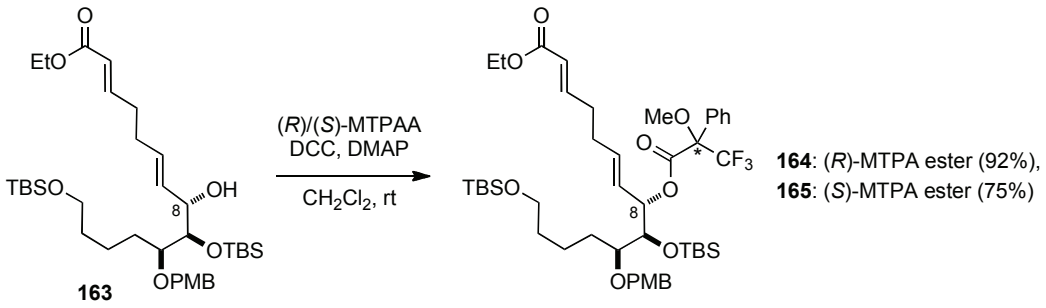


Figure 3.8.1 Evans-Cornforth model for diastereoselective reduction.

The stereochemistry of the C8 hydroxyl was confirmed after the synthesis of *(R)/(S)*-MTPA ester derivatives **164** and **165** (Table 3.8.1). Analysis of the *(R)/(S)*-MTPA

^{1}H NMR spectra according to the advanced Mosher method, revealed the H1-H7 protons shielded in the *(S)*-MTPA ester **165** thus giving negative values after deduction, the H8-H14 protons returned positive values due to being moved upfield in the *(R)*-MTPA ester **164**, providing proof for the C8*S* configuration. With the successful installation of the C8 stereocentre and confirmation of its configuration, the C8-C10 stereotriad has been completed with high levels of diastereo- and enantiocontrol.

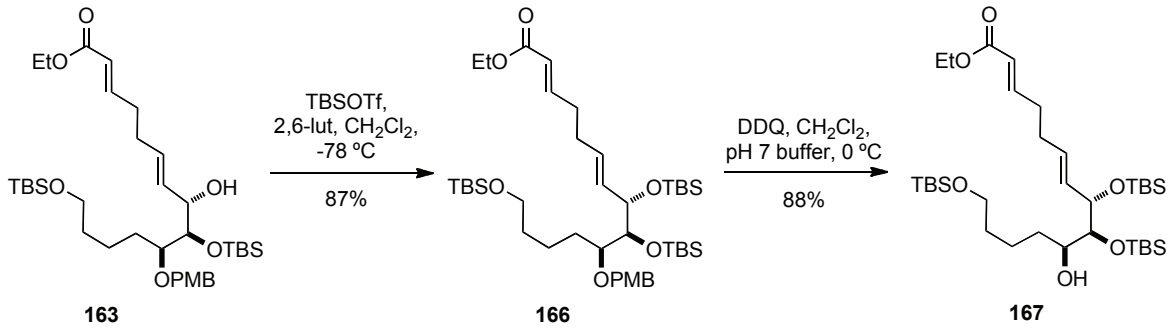


Assignment	δ_S/ppm	δ_R/ppm	$\delta_S - \delta_R$/ppm
H-6	5.67	5.78	-0.11
H-7	5.44	5.54	-0.10
H-8	5.60	5.55	0.05
H-9	3.77	3.76	0.01
H-10	3.31	3.25	0.06

Table 3.8.1 Formation of the *(R)*- and *(S)*-MTPA esters 164 and 165, and ^{1}H NMR analysis.

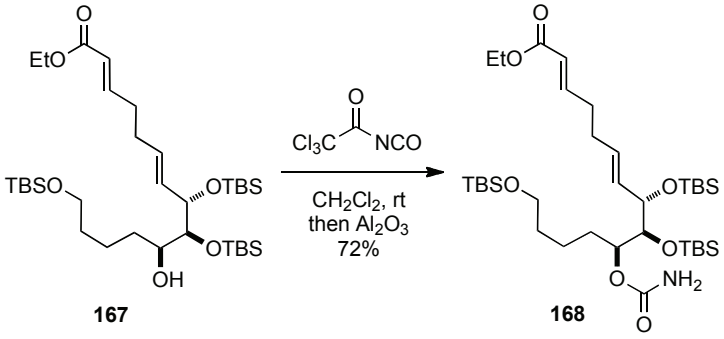
3.8.2 Synthesis of the C1-C14 aldehyde

Following the enone reduction, the newly formed C8 hydroxyl in **163** was protected as its TBS ether employing TBSOTf and 2,6-lutidine to provide **166** in 87% yield (Scheme 3.8.2). In order to minimise the number of synthetic operations on the advanced material and taking into consideration the challenges in removing the PMB ether in the presence of the C14-C17 diene encountered by Hall *et al.* during the synthesis of palmerolide A **4**,[8] it was decided to introduce the C10 carbamate at this stage. Therefore, DDQ deprotection of the PMB-ether of **166** revealed the C10 hydroxyl, providing **167** in 88% yield (Scheme 3.8.2).



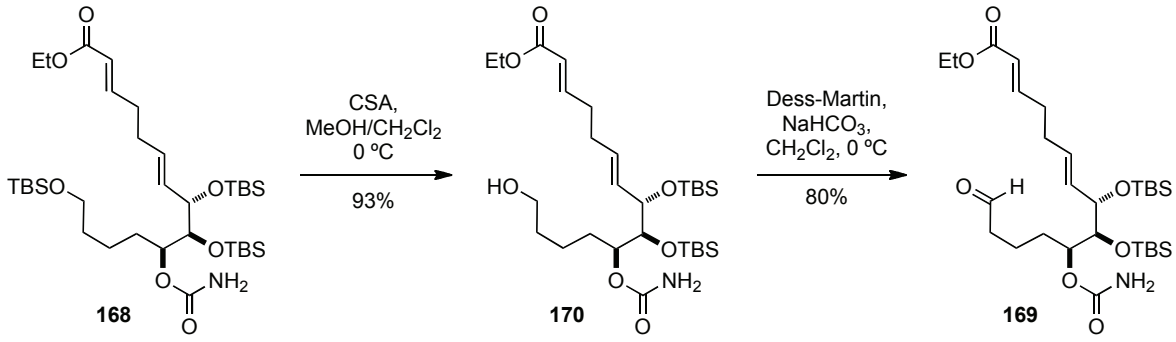
Scheme 3.8.2 Protection/deprotection to form C10 alcohol 167.

With compound **167** in hand, installation of the carbamate at the C10 position was required. The employed procedure utilised trichloroacetyl isocyanate[101] to form the corresponding trichloroacetyl carbamate, subsequent hydrolysis on neutral alumina followed by filtration provided unsubstituted carbamate **168** in excellent 72% yield (Scheme 3.8.3).



Scheme 3.8.3 Formation of the carbamate 168.

To complete the synthesis of C1-C14 fragment **169** (Scheme 3.8.4), the primary TBS ether in **168** was cleaved under acidic conditions in a 6 : 1 mixture of CH_2Cl_2/MeOH, which proved optimal for selective deprotection. The alcohol **170** was obtained in excellent 93% yield, and subsequent oxidation with Dess-Martin reagent afforded the C1-C14 aldehyde **169** in 80% yield.



Scheme 3.8.4 Completion of the C1-C14 aldehyde 169.

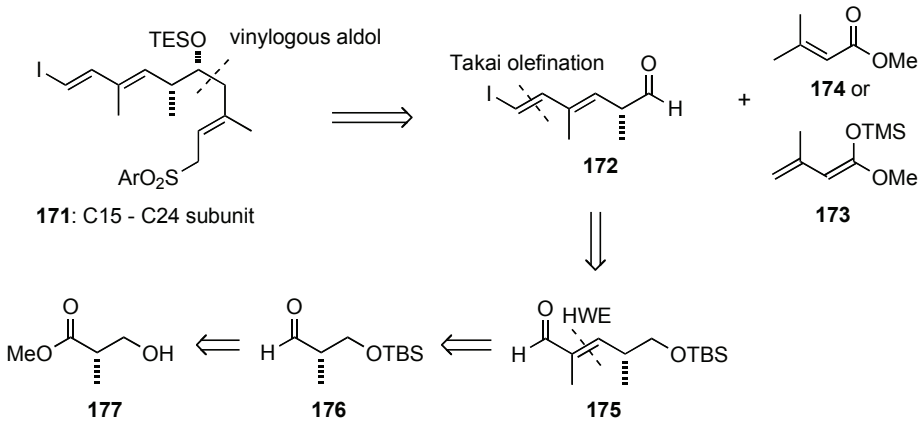
3.9 Summary

The C1-C14 subunit **169** was completed in seventeen steps from the proline-aldol reaction of ketone **63** and aldehyde **84** in 6% overall yield. Although, the first organocatalytic transformation provided product **86** in moderate yield, the remaining synthetic operations proved to be very efficient and reliable. Further complexity elements such as the installation of the C8 stereocentre with required *(S)* stereochemistry and introduction of the C10 carbamate functionality were successfully achieved.

Chapter 4

4.1 Retrosynthetic analysis of the C15-C24 fragment 171

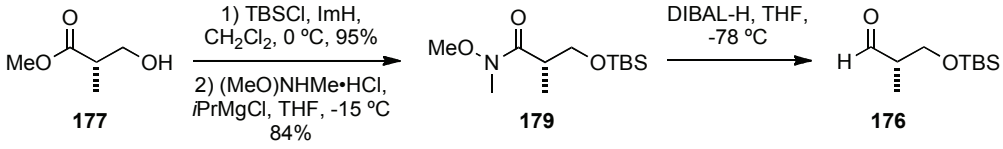
In planning the synthesis of the C15-C24 fragment **171** (Scheme 4.1.1), a vinylogous aldol disconnection was viewed as the most efficient approach. This required an α-chiral aldehyde **172** bearing the sensitive dienyl-iodide functionality and the corresponding silyl ketene acetal **173** or enolate of acrylate **174**. By choosing this disconnection, selective installation of the C19 stereocentre could be fully addressed. Either employing Yamamoto's vinylogous aldol reaction between **172** and **174** where bulky Lewis acid aluminum tris-(2,6-diphenyl)-phenoxide (ATPH) would control regio-selectivity, or a vinylogous Mukaiyama aldol reaction of **172** and **173**, the stereoselectivity would depend on Felkin-Anh control.[102,103] The synthetic design based on this disconnection would reveal divinyl iodo-aldehyde **172**, which would be accessed *via* Takai olefination of aldehyde **175**. Enal **175**, would arise from a HWE reaction of aldehyde **176**, which could be prepared from methyl (2*S*)-3-hydroxy-2-methylpropionate **177**, commonly known as Roche ester.



Scheme 4.1.1 Retrosynthetic analysis of C15-C24 fragment 171.

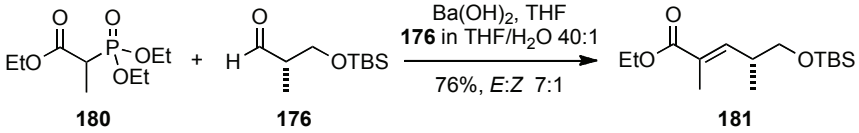
4.2 Preparation of the vinyl iodo-alcohol 178

The synthesis of the C15-C24 subunit **171** began with the three-step synthesis of aldehyde **176**. Treatment of (*S*)-Roche ester **177** with TBSCl and imidazole in dichloromethane provided derivative of **177** (Scheme 4.2.1). Subsequent formation of the Weinreb amide **179** *via* reaction with Weinreb salt and *i*-propylmagnesium chloride in tetrahydrofuran, followed by DIBAL-H reduction of **179** provided aldehyde **176**,[73] which was used immediately in the HWE reaction (Scheme 4.2.1).



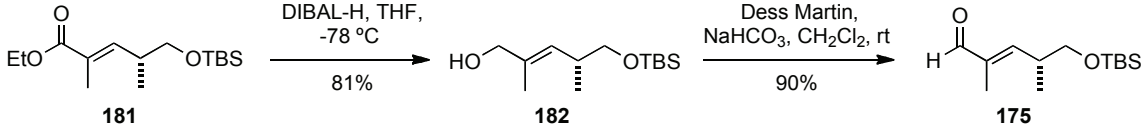
Scheme 4.2.1 Preparation of TBS-protected aldehyde 176.

The freshly prepared aldehyde **176** was used in a HWE reaction with triethyl 2-phosphonopropionate **180** and barium hydroxide (Scheme 4.2.2).[104] The formation of trisubstituted enoate **181** was achieved in 76% yield from intermediate **179** with good *E* : *Z* selectivity (7 : 1). Studies performed by Sinisterra provided some insight into the mechanism and selectivity of the reaction. He found that the interfacial solid-liquid interactions between the substrate and microcrystalline structure of the barium hydroxide were critical to that system.[105]



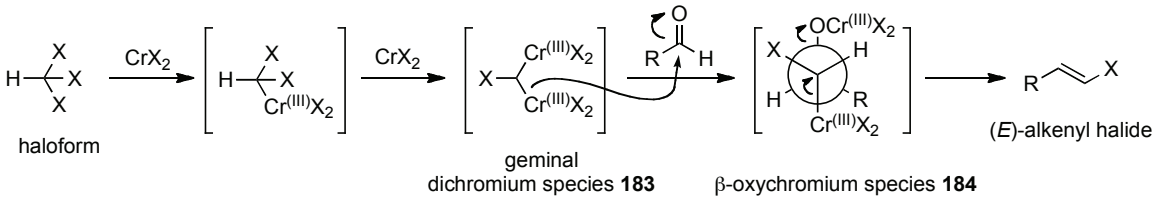
Scheme 4.2.2 Horner-Wadsworth-Emmons olefination to form enoate 181.

Treatment of the enoate **181** with DIBAL-H provided alcohol **182** in 81% yield, which was readily separated from the remaining *Z*-isomer. Subsequent oxidation using Dess-Martin periodinane afforded aldehyde **175** in 90% yield (Scheme 4.2.3).



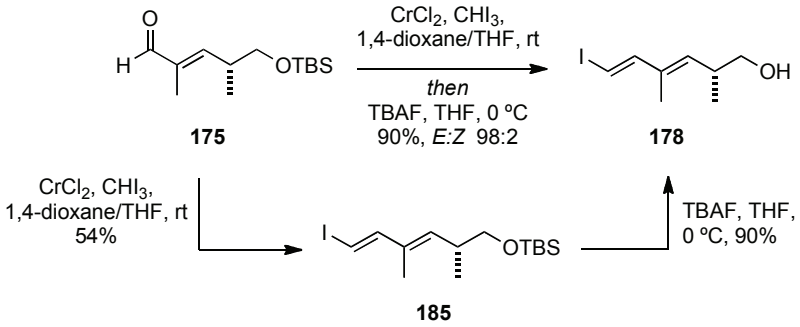
Scheme 4.2.3 Formation of the aldehyde 175.

The stage was now set for the introduction of the vinyl iodide moiety. Takai olefination would provide direct access to the vinyl iodide and it generally proceeds in high yield and with good *(E)*-selectivity.[37] In principle, this process involves the chromium(II)-mediated one-carbon homologation of an aldehyde with haloform to provide the corresponding vinyl halide. Takai and Utimoto suggested that the haloform first reacts with chromium to form a nucleophilic geminal-dichromium species **183** which attacks the aldehyde (Scheme 4.2.4)[37] and the *(E)*-alkene is formed from the β-oxychromium intermediate **184**. The rate of the reaction and selectivity are dependant on the haloform employed and increases in the order of Cl < Br < I.



Scheme 4.2.4 Proposed mechanism of Takai olefination.

Thoroughly flame-dried chromium chloride was suspended in tetrahydrofuran (care was taken to mechanically agitate the suspension to ensure that it had not fused) and the mixture of aldehyde **175** and iodoform in 1,4-dioxane was added dropwise over one hour. Although the corresponding product **185** was formed within an hour, as indicated by TLC, the purification by column chromatography significantly reduced the yield of isolated **185** (Scheme 4.2.5). In order to overcome this problem, direct deprotection with TBAF was performed to provide iodo-alcohol **178** in 90% yield. Upon comparison of different trials of a Takai olefination, it was noticed that the concentration and ratio of 1,4-dioxane : THF was critical to reaction yield and selectivity. The best yield with exclusive *(E)* product **178** was obtained when 7 : 1 mixture of 1,4-dioxane : THF was used, under strictly anhydrous conditions. It is worth noting that the obtained product **178** could only be stored for short period of time at low temperatures, with the exclusion of light.



Scheme 4.2.5 Formation of the iodo-alcohol 178.

4.3 Vinylogous Yamamoto aldol reaction

With iodo-alcohol **178** in hand attention turned towards the construction of the C18-C19 bond. The initial plan envisioned a Yamamoto vinylogous aldol reaction using aluminum tris-(2,6-diphenyl)-phenoxide (Figure 4.3.1) as a Lewis acid to build up the required C18-C19 connection.

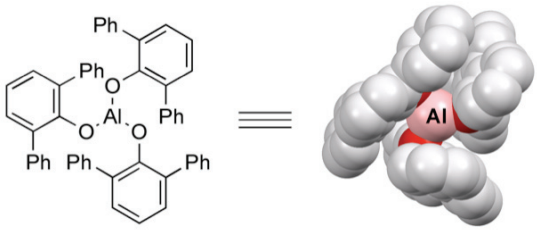
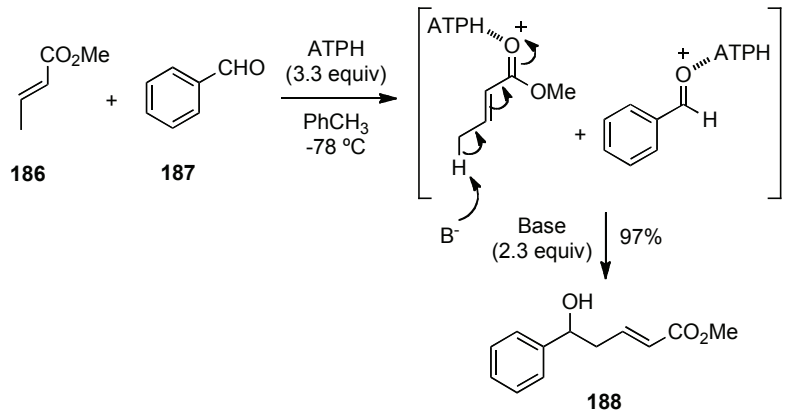


Figure 4.3.1 Yamamoto bulky Lewis acid ATPH.

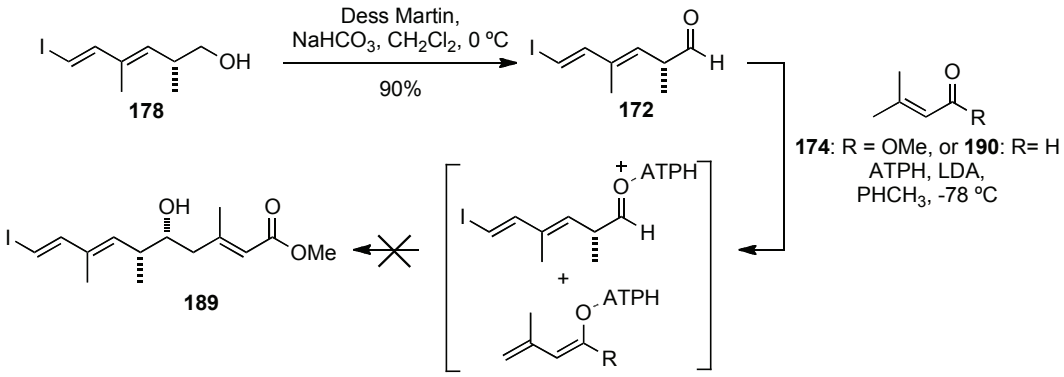
This transformation is dependant on the host properties of the bulky Lewis acid ATPH for carbonyl guests. The ATPH and carbonyl compounds self-assemble to form complexes where the carbonyl can either be protected towards nucleophilic addition or activated towards selective transformations unattainable under normal conditions. Complexation of an equimolecular mixture of an unsaturated enolisable enoate **186** and an aldehyde **187** with ATPH encapsulates the carbonyl substrates in the cavity of the Lewis acid, shielding their α-carbons (Scheme 4.3.1). The sterically accessible γ-proton can then be deprotonated selectively by a bulky base such as lithium diisopropylamide (LDA), affording an extended enolate which then adds in a γ-1,2-fashion to the aldehyde **187** giving product **188** in 97% yield.[106-109]



Scheme 4.3.1 Yamamoto vinylogous aldol reaction.

Investigation of the Yamamoto protocol began with oxidation of the alcohol **178** using Dess-Martin reagent[110,111] to provide aldehyde **172** in 90% yield. The isolation of the aldehyde **172** proved challenging as it readily decomposed on exposure to light. In order to minimise this exposure, rapid purification of the reaction mixture through a short pad of silica/celite gel, followed by solvent removal and drying under reduced pressure in the dark provided access to **172**.

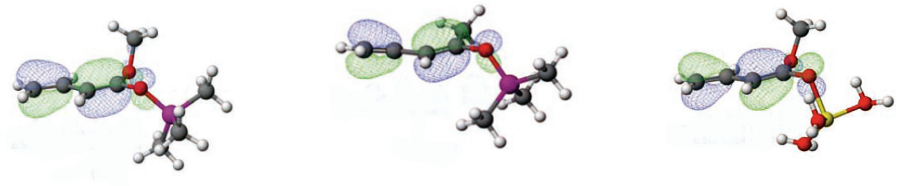
Aldehyde **172** was then added to the freshly prepared mixture of ATPH and methyl 3,3-dimethylacrylate **174** in toluene at -78 ºC. Upon complexation, a freshly prepared solution of LDA was added to the reaction mixture (Scheme 4.3.2). Despite several attempts of the reaction with the highest-purity reagents, no coupled product **189** was observed. Attempts to use aldehyde **190** instead of acrylate **174**, also failed to deliver the desired product, only decomposition of the iodo-aldehyde **172** occurred.



Scheme 4.3.2 Attempted vinylogous Yamamoto aldol reaction to form 189.

4.4 Vinylogous Mukaiyama aldol reaction

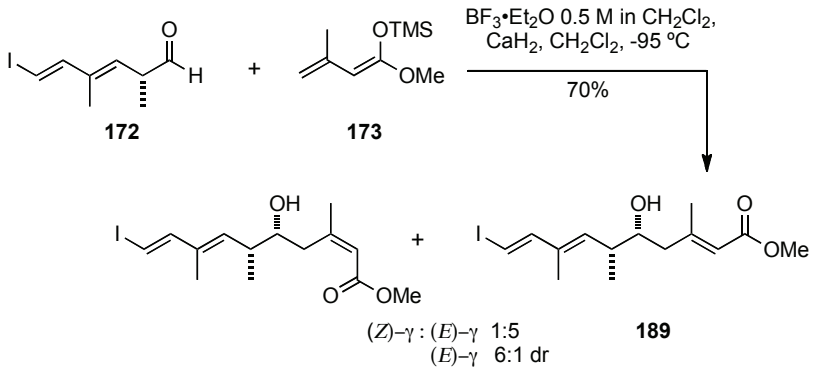
Attention was then focused on the investigation of a vinylogous Mukaiyama aldol reaction (VMAR) between the silyl ketene acetal **173** and aldehyde **172**.[112] The observed regioselectivity in this reaction can be rationalised upon consideration of the electronic and steric effects of the silyl ketene acetal **173**. As described by Denmark,[113] **173** is a highly electron rich species and its reactions are governed by electrostatic interactions. Relying on the computational calculations for the orbital coefficients (O.C.) and electrophilic susceptibilities (E.S.) of **173** and similar species (silyl enol ether **190**, lithium enolate of the methyl crotonate **191**), Denmark postulated that γ-selectivity could be predicted due to the higher electron density observed around C4 rather than the C2 position (Figure 4.4.1). Steric effects contribute to the site selectivity; C2 in **173** is a more sterically hindered site owing to its proximity to the silyl group and the alkyl group of the ester. Therefore, the approach of the electrophile to the less sterically demanding C4 position is favoured when C4 is not similarly substituted.[113]



silyl ketene acetal **173**	silyl enol ether **190**	lithium dienolate **191**
C4 C3 C2 C1	C4 C3 C2 C1	C4 C3 C2 C1
O.C: 0.302, 0.090, 0.230, 0.219	O.C: 0.280, 0.083, 0.243, 0.235	O.C: 0.289, 0.042, 0.311, 0.130
E.S: 0.592, 0.177, 0.451, 0.429	E.S: 0.550, 0.165, 0.478, 0.461	E.S: 0.572, 0.084, 0.614, 0.257

Figure 4.4.1 Structures of silyl ketene acetal 173, silyl enol ether 190 and lithium dienolate 191, reproduced from ref [113].

With the aldehyde **172** in hand, the investigation of the VMAR began. A solution of **172** in dichloromethane and silyl ketene acetal **173** in the presence of calcium hydride was cooled down to -95 ºC. Dropwise addition of the BF_3•Et_2O solution in dichloromethane and controlled elevation of the temperature to allow the reaction to occur, but not above -80 ºC, promoted the formation of the aldol adduct **189** (Scheme 4.4.1). Under the optimised conditions, the α-regioisomer was not observed and stereoisomers of the γ-product were isolated in total 70% yield with an *E* : *Z* ratio of 5 : 1 and *syn* : *anti* 6 : 1 for the major *(E)*-diastereoisomer.



Scheme 4.4.1 Vinylogous Mukaiyama aldol reaction to form 189.

The selectivity of the newly installed C19 stereocentre arose from Felkin-Anh addition to the α-chiral aldehyde **172**.[102,114] The transition state **TS I** presented in Figure 4.4.2 shows the approaching nucleophile with respect to the Bürgi-Dunitz trajectory. The carbonyl compound placed with the largest substituent perpendicular to the C=O group and excluding all possible eclipsing interactions.

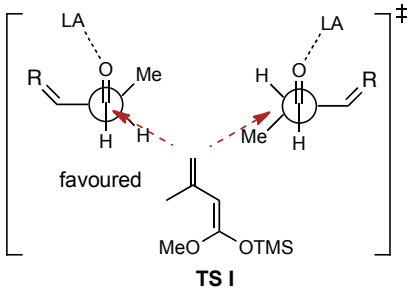
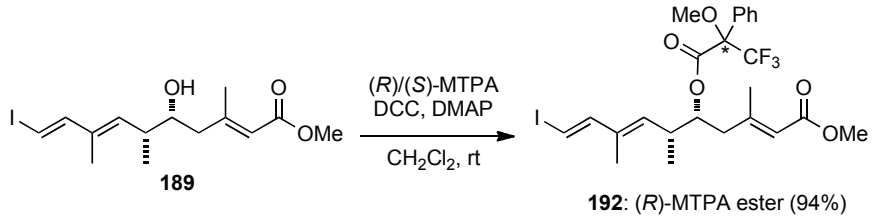


Figure 4.4.2 Felkin-Ahn controlled addition of silyl ketene acetal 173 to the α-chiral aldehyde 172.

Confirmation of the C19 hydroxyl stereochemistry was provided by Mosher ester analysis (Table 4.4.1). Accordingly shifted protons in *(R)*- and *(S)*-MTPA esters **192** and **193** returned positive values for H16 to H18 and negative values for H20 to H24 confirming the expected *(R)*-configuration of the C19 stereocentre in **189**, consistent with the VMAR proceeding with good levels of Felkin-Anh control.

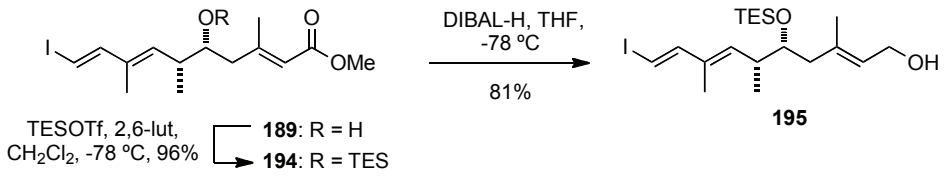


Assignment	δ_s/ppm	δ_r/ppm	$\delta_s - \delta_r$/ppm
H-16	5.68	5.61	0.07
H-18a	2.45	2.41	0.04
H-18b	2.43	2.42	0.01
H-19	5.23	5.23	0.00
H-20	2.73	2.82	-0.09
H-21	5.14	5.26	-0.12
H-23	6.92	7.01	-0.09
H-24	6.23	6.28	-0.05

Table 4.4.1 Formation and analysis of the *(R)*- and *(S)*-Mosher esters 192 and 193.

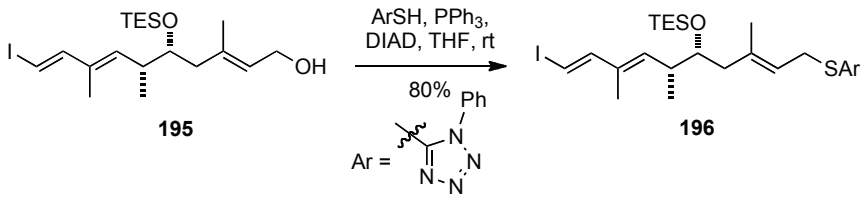
4.5 Completion of C15-C24 fragment 171

Having successfully installed the C18-C19 connection with requisite C19 stereochemistry, all that remained to complete sulfone **171** was C19 protection and manipulation of the C15 terminus. The C19 hydroxyl of **189** was protected using triethylsilyl triflate and 2,6-lutidine to form enoate **194** in excellent yield (Scheme 4.5.1). Subsequent reduction of the ester moiety with DIBAL-H afforded allylic alcohol **195** in 81% yield (Scheme 4.5.1).



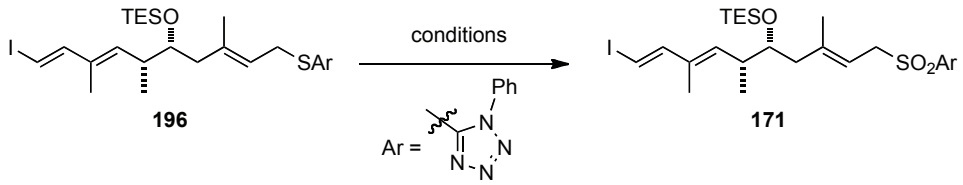
Scheme 4.5.1 Formation of the allylic alcohol 195.

Introduction of the sulfide functionality was accomplished under Mitsunobu conditions with 1*H*-mercaptophenyltetrazole to provide compound **196** in 80% yield (Scheme 4.5.2). Given the reliable sequence to the advanced synthetic intermediate of the C15-C24 fragment **171**, we were now approaching the oxidation of sulfide **196** to complete the Julia-Kocienski coupling partner.



Scheme 4.5.2 Mitsunobu reaction introducing sulfide 196.

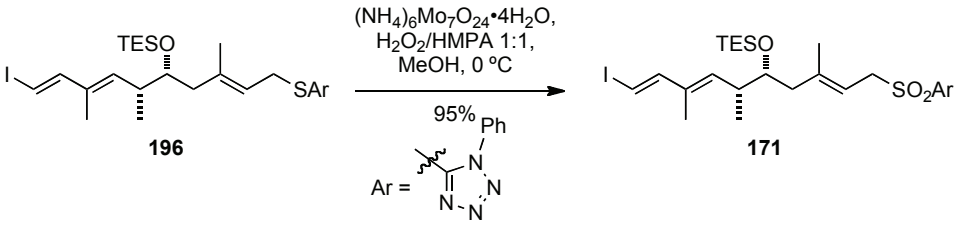
The ammonium molybdate-catalysed oxidation with hydrogen peroxide was investigated first and unfortunately it had a destructive effect on the starting material **196** (Table 4.5.1, entry 1). We then examined different solvents in combination with hydrogen peroxide and molybdenum salt (Table 4.5.1, entries 2-4). In all conditions investigated sulfone **171** was not formed and either sulfide **196** decomposed under the reaction conditions or was partly recovered. Treatment of the substrate **196** with Oxone® in a mixture of water and methanol at 0 ºC did not promote formation of the desired product **171**, although starting material was recovered (Table 4.5.1, entry 5). The procedure utilising catalytic scandium triflate in combination with hydrogen peroxide was then attempted and resulted in sulfoxide formation, and sulfone **171** was not detected in the reaction mixture (Table 4.5.1, entry 6).



Entry	Reagent	Solvent	Temp.	Yield (%)
1	20 mol%$(NH_4)_6Mo_7O_{24}$•$7H_2O$, 10 eq. H_2O_2	EtOH	0 ºC - rt	decomp.
2	10 mol%$(NH_4)_6Mo_7O_{24}$•$7H_2O$, 5 eq. H_2O_2	EtOH	0 ºC	decomp.
3	1 mol%$(NH_4)_6Mo_7O_{24}$•$7H_2O$, 10 eq. H_2O_2	EtOH/THF 1:1	0 ºC	st. mat. **196** (50%)
4	10 mol%$(NH_4)_6Mo_7O_{24}$•$7H_2O$, 10 eq. H_2O_2	EtOH/DCM 1:1	0 ºC	st. mat. **196** (50%)
5	3 eq. Oxone	MeOH/H_2O 1:3	0 ºC - rt	st. mat. **196** (50%)
6	20 mol% $La(OTf)_3$, 20 eq. H_2O_2	CH_2Cl_2/EtOH 9:1	0 ºC	sulfoxide

Table 4.5.1 Oxidation of sulfide 196.

Vedejs'[115] studies on stabilisation of the peroxy-molybdenum complexes by the hexamethylphosphoroamide (HMPA) prompted the investigation of the initially studied conditions (Table 4.5.1, entry 2), but in the presence of HMPA. The performed protocol employing 10 mol% of ammunium molybdate hydrate with 10 equivalents of the hydrogen peroxide relative to the substrate **196** was premixed with HMPA (v/v). The bright yellow solution was then added dropwise to a 0.1 M solution of sulfide **196** in methanol at 0 ºC (Scheme 4.5.3). The reaction mixture was stirred for 24 hours in an ice-water bath providing the desired sulfone **171** upon aqueous work-up and column chromatography. While this procedure proved to be reliable and convenient on a small scale (up to 0.2 mmol of **196**), no full conversion of starting material **196** and partial decomposition was observed when reaction was carried out on bigger quantities (>0.2 mmol of **196**). Nonetheless, performing the reaction in parallel on an adequate scale (<0.2 mmol of **196**) produced a satisfactory amount of sulfone **171**.



Scheme 4.5.3 Molybdenum catalysed oxidation to sulfone 171.

4.6 Summary

The western hemisphere of palmerolide C, the C15-C24 subunit **171** was synthesised in fourteen steps in 16% overall yield starting from the Weinreb amide derivative of (*S*)-Roche ester **177**. The crucial transformation to build the C18-C19 bond relied on Mukaiyama vinylogous aldol reaction, which allowed for controlled introduction of the C19 stereocentre and was compatible with a sensitive iodo-aldehyde **172**. Final oxidation of sulfide **196** was achieved after the addition of HMPA to the ammonium molybdate-catalysed reaction with hydrogen peroxide.

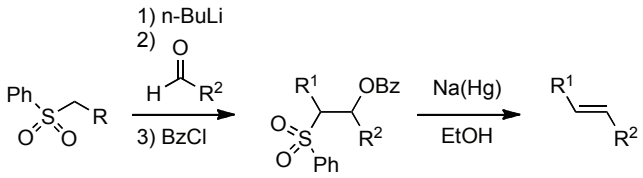
Chapter 5

5.1 C1-C14 and C15-C24 fragment union

Having completed the synthesis of the C1-C14 and C15-C24 subunits **169** and **171**, investigation of their coupling reaction began. As outlined in our retrosynthesis, the Julia-Kocienski olefination coupling would be employed as an efficient approach to construct the C14 *E* alkene of the C14-C17 diene.

5.1.1 Introduction to the Julia olefination

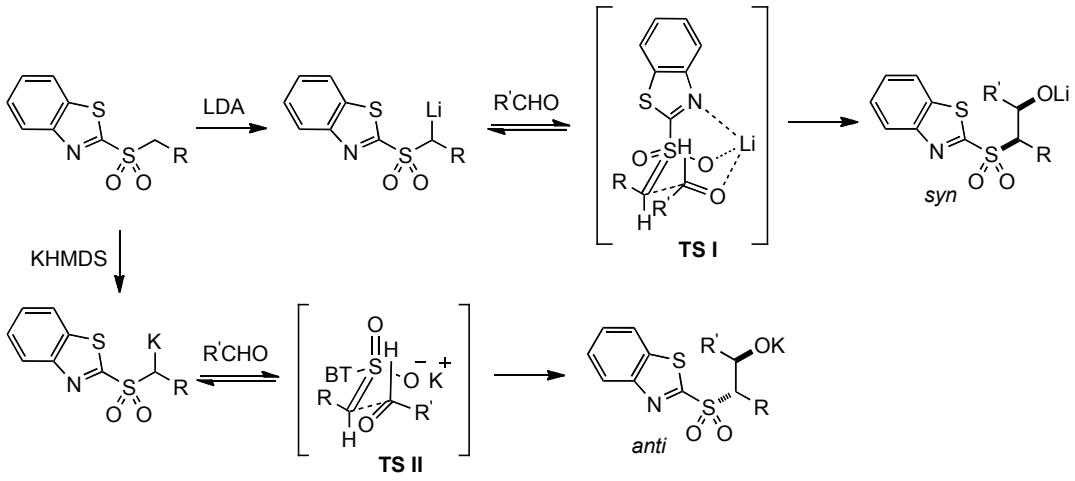
In 1973 Julia *et al*. reported a process to form a C—C double bond using a phenyl sulfone anion and carbonyl compounds involved a sequence of several synthetic operations: addition, acylation of the resulting β-alkoxysulfone and reductive elimination of the β-acyloxysulfone with Na(Hg) or SmI_2 (Scheme 5.1.1).[116]



Scheme 5.1.1 Olefination reaction between phenyl sulfone and aldehyde developed by Marc Julia.

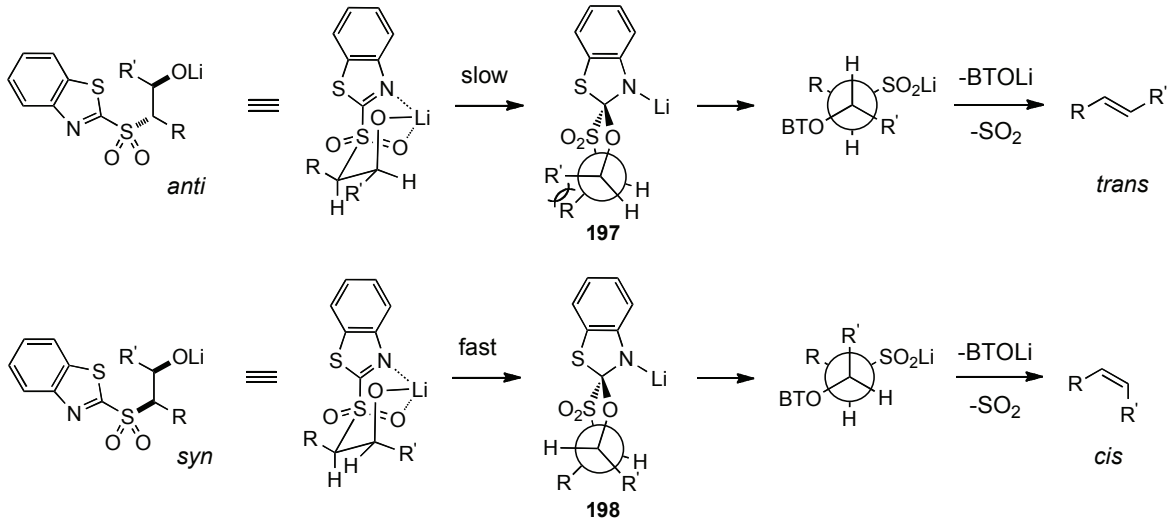
The modified Julia reaction developed by Julia,[117] enabled the preparation of alkenes from benzothiazol-2-yl (BT) sulfones and aldehydes in a single step, but the stereochemical outcome is a direct consequence of the initial carbonyl addition (Scheme 5.1.2). Although this first step is reversible, the formation of the *anti* or *syn* intermediate might be influenced by the reaction conditions. A *syn* intermediate could be formed as a result of chelation control (**TS I**), which occurs upon addition of the base with small counterions (Li) and in an apolar solvent. The addition of base with a larger counterion (K)

in polar solvent will promote the formation of the *anti* intermediate *via* the open transition state **TS II**.[117]



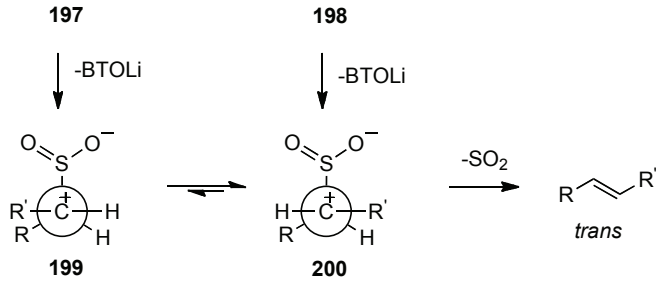
Scheme 5.1.2 Influence of the reaction conditions on modified Julia reaction with BT-sulfone.

In 1993 Julia investigated the base mediated elimination of *anti* β-hydroxy-BT-sulfones with alkyl substituents, which decompose to the *(E)*- and *(Z)*-alkenes, with noticeable propensity to form the *(Z)*-olefins. This can be explained due to the high-energy conformer **197** with the *gauche*-like arrangement of substituents forming slower than **198** (Scheme 5.1.3).[118] The initial addition of the metallated sulfone to the carbonyl compound dictates the stereochemical outcome. The observed results reflected the ratio of spiro-intermediates **197** and **198**, which upon elimination of the antiperiplanar lithium benzylthiozolone and sulfur dioxide furnished *cis*- or *trans*-olefins. However, when β-hydroxy-BT-sulfones with R' vinyl/aryl substituents were examined, the tendency towards *(E)*-olefin formation was observed. If equilibration of the intermediates is precluded, there must be different mechanism effecting predominant formation of the *(E)*-configured olefins.



Scheme 5.1.3 Mechanism of modified Julia reaction.

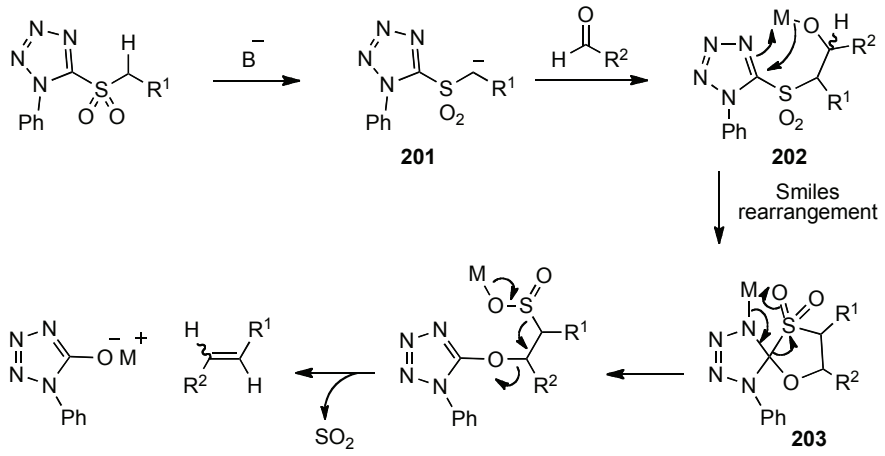
This is explained by the direct loss of the lithium benzylthiozolone from intermediates **197** and **198** (or a similar event immediately following spirocycle opening) yielding zwitterionic conformers **199** and **200** (Scheme 5.1.4). Equilibration of the betaine intermediates towards the more energetically favoured conformer **200**, provides an (*E*)-alkene product upon loss of sulfur dioxide. Unsaturated residues in R' provide stabilisation for the carbenium ion present in **199**/**200** and therefore promote the suggested pathway.[119]



Scheme 5.1.4 Mechanistic rational for observed selectivity in the modified Julia reaction.

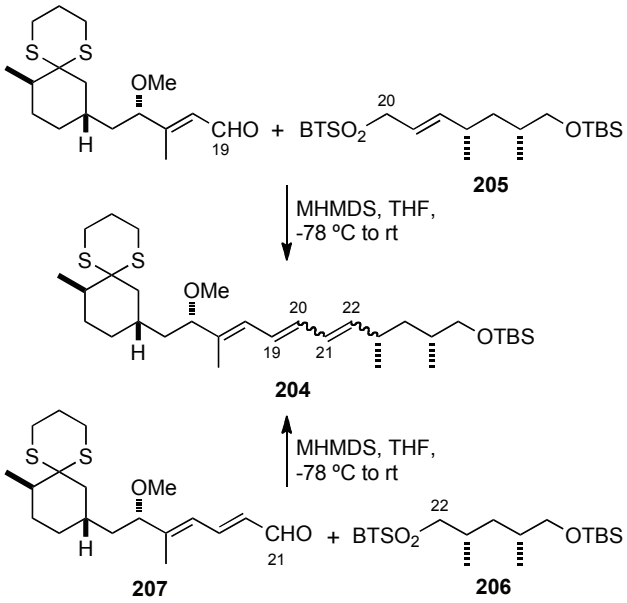
The Julia-Kocienski olefination is a later modification of the Julia reaction. Kocienski's studies resulted in the development of an *(E)*-alkene selective system utilising phenyltetrazolyl sulfone (PT) instead of benzothiazolyl (BT) sulfone. Later, Blakemore extended the library of heteroaromatic sulfones compatible with Julia reaction to 1-isoquinolinoyl, 1-methyl-2-imidazolyl, 4-methyl-2-imidazolyl and 4-methyl-1,2,4-triazol-3-yl sulfones.[120]

Kocienski observed that the 1-phenyl-1*H*-tetrazol-5-yl sulfone anion **201** was not prone to self-condensation, therefore it could first be deprotonated with base (**201**) and then reacted with an aldehyde (Scheme 5.1.5). This extended the scope of compatible carbonyl substrates, including reactions with base-sensitive aldehydes. The transient β-alkoxysulfone **202** reacts further to form spiro-intermediate **203**, which breaks down *via* a Smiles rearrangement to deliver the olefinic product with extrusion of sulfur dioxide and lithium phenyltetrazolone. An increase in *(E* : *Z)* ratio was generally observed upon changing the counter-ion (Li < Na < K) of the base. In addition, an increase in polarity and coordinating ability of the solvent (PhMe < Et_2O < THF < DME) favours formation of the *(E)*-alkene.[121]



Scheme 5.1.5 Mechanism of Julia-Kocienski reaction.

In 1996, Kocienski reported the synthesis of the C10-C26 fragment **204** of rapamycin,[122] investigating substrate dependent aspects of the selectivity in Julia olefination. As shown in Scheme 5.1.6, selective formation of the triene portion of **204** was significantly influenced by the choice of starting materials. This study demonstrated that while using BT-sulfone **205**, the *(Z)*-olefin was formed preferentially, which supports the hypothesis that stabilised BT-sulfone anions have a tendency to form *(Z)*-configured products. When sulfone **206** was used together with conjugated aldehyde **207**, formation of the *(E)*-olefin was observed with almost complete selectivity when LiHMDS was employed.



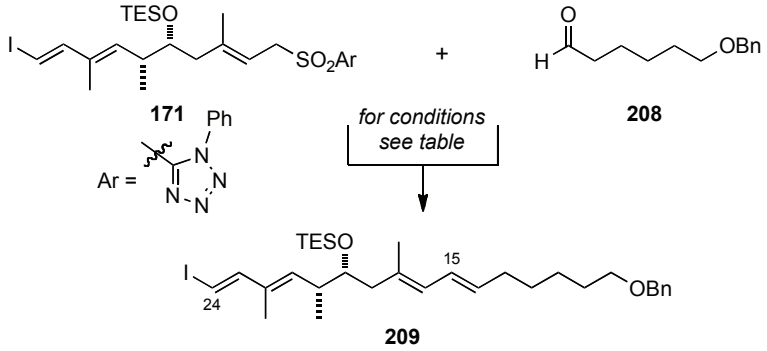
M	Yield (%)	*E* : *Z*
Li	75	29 : 71
Na	79	43 : 57
K	--	18 : 82

M	Yield (%)	*E* : *Z*
Li	68	95 : 05
Na	21	78 : 22

Scheme 5.1.6 Substrate dependence in modified Julia reaction.

5.1.2 Model system for Julia-Kocienski coupling

Given the lengthy synthesis of aldehyde **169** it was decided to pursue model studies to develop the optimal conditions for the olefination reaction. Using sulfone **171** and benzyl-protected aldehyde **208** as a model substrate, a range of reaction conditions were explored as summarised in Table 5.1.1. It was initially thought that by reacting the anion of sulfone **171** with an excess of aldehyde **208** would assure complete formation of the coupled product **209** (Table 5.1.1, entry 1, 2). However, unreacted sulfone **171** was always recovered upon purification, delivering only small amount of the diene **209**, regardless of the solvent used. When an excess of sulfone **171** in combination with 1.3 equivalents of base was reacted with a 1.0 equivalent of aldehyde **208**, instant formation of the product **209** was detected by TLC (Table 5.1.1, entry 3). Prior to the aqueous work-up the reaction mixture was quenched by the addition of a few drops of methanol, consequently the product **209** was isolated in 80% yield. Following the assignment by ^{1}H-^{1}H COSY experiment, ratio of the *(E)*- and *(Z)*-isomers was determined by analysis of ^{1}H NMR. Diagnostic C15 resonance *J* value for *(E,E)*-diene were 15.0 and 10.8 Hz, whereas the *(Z)*-olefin showed a smaller coupling constant at 6.2 Hz, both values were consistent with the *J* coupling constants reported for *(E)*- and *(Z)*-2-methylhexa-2,4-diene at 14.4 and 5.6 Hz respectively.[123]

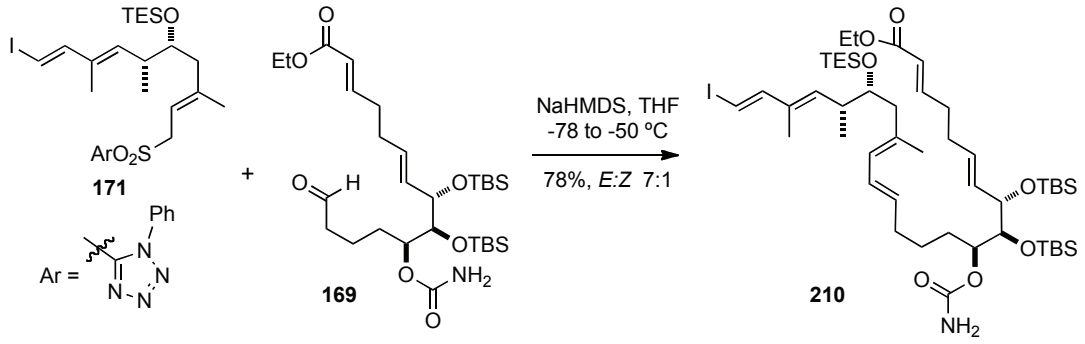


Entry	171: 208 (eq)	Base (eq)	Solvent	Temp. (ºC)	Yield (%, *E*:*Z*)
1	1 : 1.5	NaHMDS (1.3)	THF	-78 to -50	10 (2 : 1)
2	1 : 1.5	NaHMDS (1.3)	DME	-78 to -50	5 (2 : 1)
3	1.5 : 1	NaHMDS (1.3)	THF	-78 to -50	80 (2 : 1)

Table 5.1.1 Julia-Kocienski coupling reaction, model studies.

5.1.3 C14-C15 bond formation *via* Julia-Kocienski coupling

The optimised conditions were now translated to the real system. In the event, deprotonation of the sulfone **171** with NaHMDS in THF at -78 ºC was followed by addition of aldehyde **169** (Scheme 5.1.7). The reaction was allowed to warm to -50 ºC within one hour and then quenched with methanol. Aqueous work-up and subsequent column chromatography provided the C1-C24 carbon framework **210** of palmerolide C in 78% yield with 7 : 1 *(E* : *Z)* selectivity. The improved selectivity compared to the model system might be attributed to the higher complexity and steric demand of the aldehyde component. Confirmation of the olefin geometry, as in the model study, was revealed upon the inspection of the ^{1}H NMR spectra of **210**. The *J* coupling constant values for the C15 resonance were found to be 15.0 and 10.8 Hz. These values were in good agreement with the values reported for the analogous system in the synthesis of palmerolide A.[6]



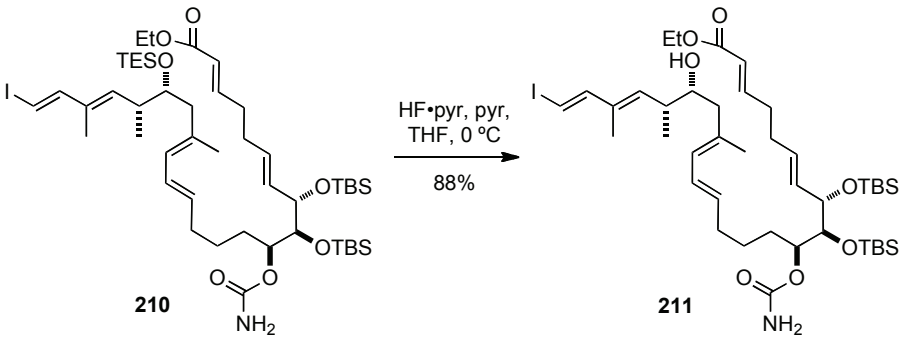
Scheme 5.1.7 Formation of the C1-C24 carbon backbone of palmerolide C *via* Julia-Kocienski reaction.

5.2 Advancing the palmerolide C carbon framework

With the advanced C1-C24 intermediate **210** in hand, all that remained was to close the macrocyclic ring and deprotect the C8 and C9 hydroxyl groups prior to the final installation of the enamide side chain.

5.2.1 Formation of the macrolactone

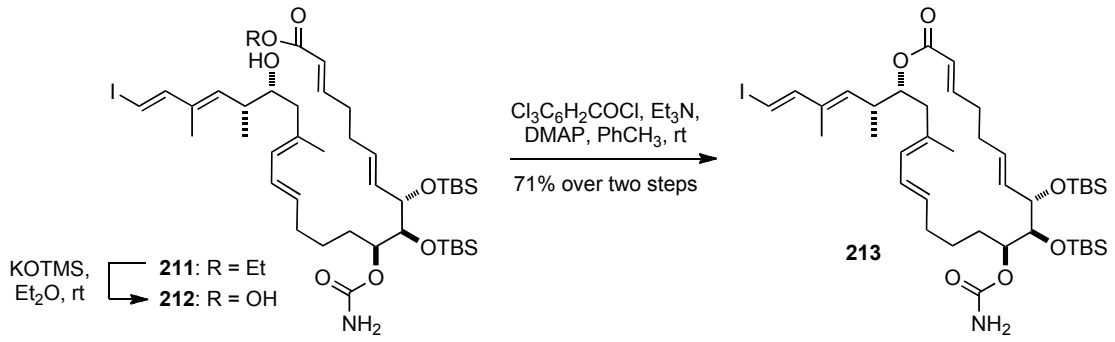
The selective cleavage of the C19 triethylsilyl group in **210** was accomplished using HF•pyridine in pyridine.[124] A reagent solution was prepared prior to the reaction by mixing 2 mL of hydrogenfluoride-pyridine complex with 4 mL of pyridine and 16 mL of THF. Column chromatography at this point enabled the separation of the C14-C15 *(E,Z)*-diene from the Julia-Kocienski coupling reaction delivering pure alcohol **211** in 88% yield (Scheme 5.2.1).



Scheme 5.2.1 Selective deprotection of the triethylsilyl protecting group to form 211.

Tentative experimentations with ester hydrolysis using potassium trimethylsilanolate[125] resulted in a poor yield of *seco*-acid **212**. The reason behind this was related to the potassium salt formed upon the reaction, which required relatively strong acidic conditions to be protonated. However, presence of the acid-sensitive conjugated iodo-diene hindered our chance of succeeding in this approach. The initially investigated aqueous work-up with ammonium chloride did not result in a formation of the expected product. The use of an aqueous citric acid work-up gave the *seco*-acid **212**, although a chromatography column to remove citrate residues was necessary. The best results were obtained upon quenching the reaction mixture with 0.1 M sodium hydrogen sulfate and subsequent addition of solid sodium sulfate. In this way, exposure to acid was minimised and filtration delivered the crude product without requirement for further purification by column chromatography. Under these optimised conditions, a mild saponification protocol employing potassium trimethylsilanolate[125] was successfully executed and upon formation of the potassium salt of **211**, acidic work-up with sodium hydrogen sulfate returned the desired *seco*-acid **212** (Scheme 5.2.2).

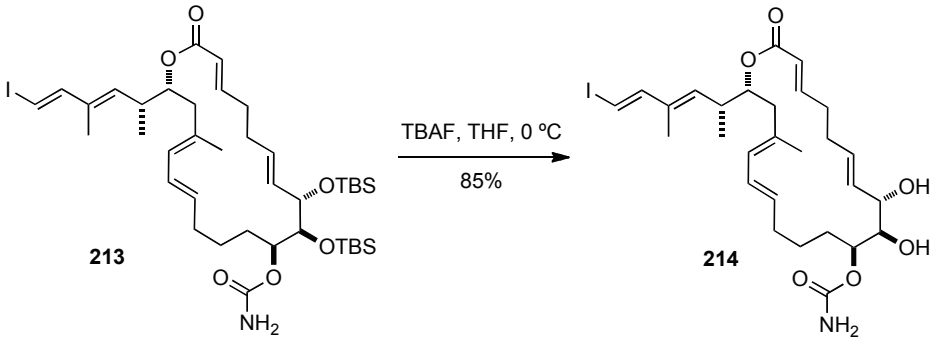
With the *seco*-acid **212** in hand, macrolactonisation under Yamaguchi conditions[31] was explored. Preparation of the mixed anhydride commenced with addition of the trichlorobenzoyl chloride to the solution of the *seco*-acid **212** and triethylamine in toluene. Upon completion, the reaction mixture was diluted and added drop-wise over three hours to a 0.001 M solution of DMAP in toluene. High dilution together with slow addition are important modifications promoting intra- rather then intermolecular esterification of the activated acid. After the addition was completed the reaction mixture was allowed to stir for a further nine hours and subsequent purification delivered macrolactone **213** in 71% yield over two steps (Scheme 5.2.2).



Scheme 5.2.2 Formation of 213 *via* Yamaguchi macrolactonisation.

5.2.2 Final deprotection

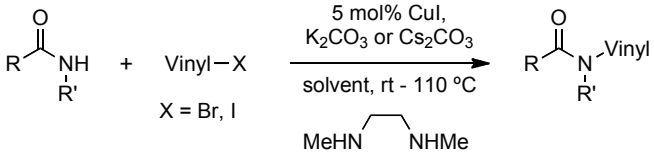
As we were approaching the final stages of the synthesis, deprotection of the remaining silyl groups was required. TBAF was chosen, as it would not affect the iodo-diene motif and was used in the final phase of palmerolide A synthesis by Hall and de Brabander. Cleavage of the C8 and C9 TBS groups in **213** was accomplished with only five equivalents of TBAF providing the direct precursor **214** to palmerolide C in 85% yield (Scheme 5.2.3).



Scheme 5.2.3 Final deprotection to deliver diol 214.

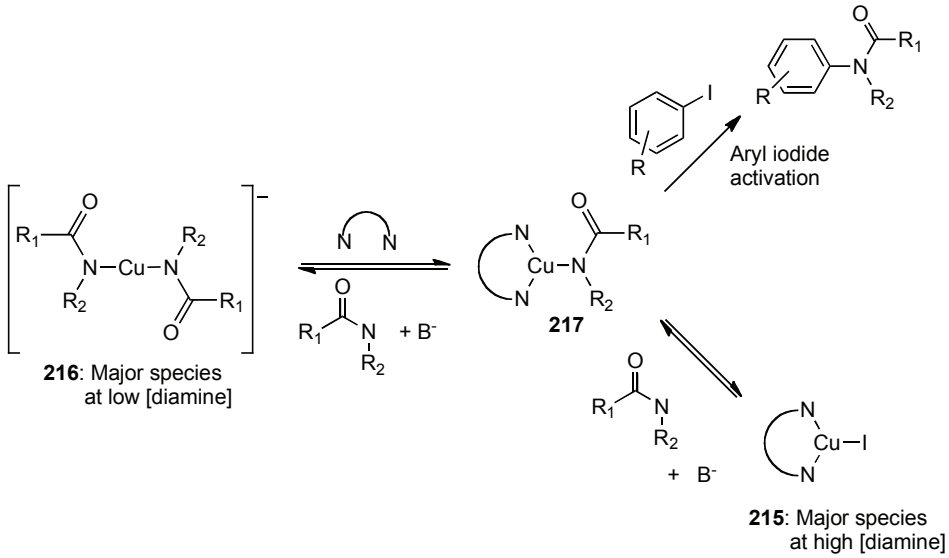
5.3 Introduction of the enamide side chain to complete palmerolide C

At this stage, we were facing the final transformation to introduce the enamide side chain. In 2003, Buchwald and Jiang reported the Goldberg-like amidation reaction of vinyl halides using copper iodide as a catalyst and *N*,*N*'-dimethylethylenediamine as a ligand.[126] They demonstrated the generality of the procedure, where a broad range of substrates with primary and secondary amides were successfully coupled with mono-, di- or tri-substituted vinyl bromides or iodides under optimised catalytic conditions (Scheme 5.3.1).



Scheme 5.3.1 Cu(I)-catalysed formation of enamides.

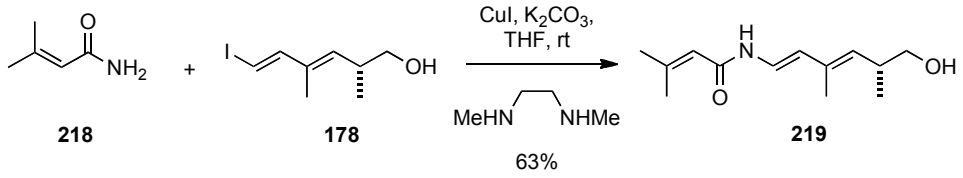
The mechanism of this transformation is not fully understood, but computational calculations and kinetic experiments performed by Buchwald provide some insight[38,127] (Scheme 5.3.2). A mechanism based on the oxidative addition/reductive elimination involving Cu(I)/Cu(III) species is proposed. The diamine ligand coordinates the CuI (**215**), therefore, prevents the ligation of the excess amide used and leaves the activation of the halide-substrate as a rate-limiting step. At low concentration of diamine, muliple ligation of the amide on copper occurs (**216**). To allow formation of the most active diamine-ligated copper(I) amidate species (**217**), the dissociation of the amide has to precede coordination to the ligand, which ultimately was identified as another rate-limiting step.



Scheme 5.3.2 Mechanism proposed by Buchwald.

As a prelude to examining this approach, the enamide formation was investigated in a model system. In accord with Buchwald protocol,[126] catalytic conditions were investigated first using iodo-alcohol **178** as a model substrate. To a mixture of **178**, freshly prepared 3,3-dimethylacrylamide **218** was added 5 mol% of copper(I) iodide, 10 mol% of *N*,*N*'-dimethylethylenediamine and 1.5 equivalents of potassium carbonate in tetrahydrofuran. However, the conditions applied did not promote formation of **219**. Following the disappointing results of the catalytic system, a stoichiometric amount of copper(I) iodide and *N*,*N*'-dimethylethylenediamine was employed. Hence, to iodo-alcohol **178** in tetrahydrofuran was added 2 equivalents of amide **218** followed by 1.5 equivalents of copper(I) iodide and an excess of potassium carbonate. The order of addition of the reagents turned out to be important, requiring the diamine ligand as the final addition,

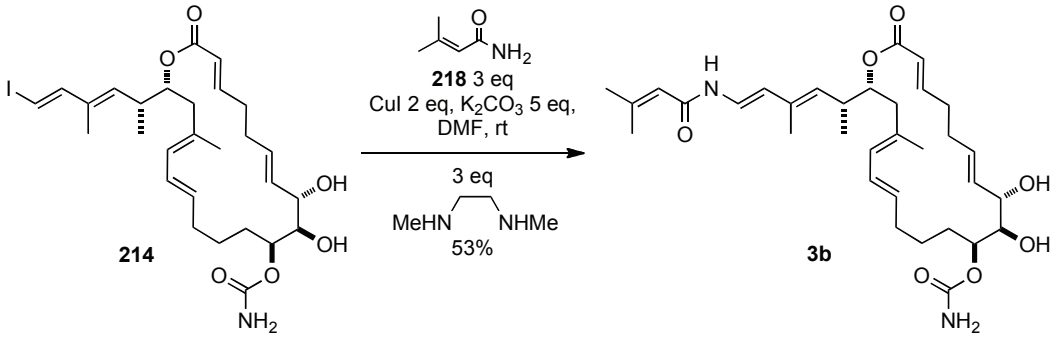
otherwise the expected product was not formed. Gratifyingly, under stoichiometric conditions the desired enamide **219** was produced in 63% yield (Table 5.3.1).



Entry	Conditions	Result
1	5 mol% CuI, 10 mol% N,N'-dimethylethylenediamine, 1.5 eq. K_2CO_3, THF, rt	—
2	1.5 eq CuI, 2 eq N,N'-dimethylethylenediamine, 5 eq. K_2CO_3, THF, rt	63%

Table 5.3.1 Buchwald enamide formation, model study.

Having established the feasibility of forming the enamide under the Buchwald conditions, efforts turned to the coupling of **214** and **218**. Direct translation of the reaction conditions developed during the model study onto substrate **214** promoted formation of the final product **3b**. Due to the solubility issues, the reaction was carried out in dimethylformamide. Subsequent purification by column chromatography provided **3b** in 53% yield and returned unreacted starting material **214** (Scheme 5.3.3).



Scheme 5.3.3 Introduction of enamide to form 3 *via* Buchwald Cu(I)-catalysed reaction.

5.4 Comparison of synthetic and natural palmerolide C

Having synthesised the target molecule **3b**, confirmation of its identity was now the focus. High resolution mass spectrometry revealed the expected ion at m/z 607.3364, which corresponds to the $[M+Na]^+$ of $C_{33}H_{48}N_2O_7Na$ and to the reported value of 607.3367. Next, the specific optical rotation was measured at a concentration of 0.2 g/mL in methanol to be -19.5, which correlates with the reported -27.1 value at a concentration

of 0.1 g/mL of methanol. The IR spectrum of the synthetic material was in good agreement with the IR of the natural palmerolide C.[21]

The ^{1}H NMR data provided for the natural sample of palmerolide C **3** was acquired in deuterated dimethylsulfoxide. Unfortunately, due to the small quantity of the synthetic material produced and the difficulties associated with sample recovery from dimethylsulfoxide, we decided to perform our first spectroscopic experiments in a different solvent. The ^{1}H and ^{1}H-^{1}H COSY NMR were carried out in acetonitrile and allowed for the structural assignment (Table 5.4.1). The initially applied parameters to obtain ^{13}C NMR were not optimal and further experiments were postponed due to the availability of sufficient time required for the analysis, and thus data was extracted from HSQC and HMBC NMR spectra.

Proton No.	Synthetic palmerolide C d_3-MeCN 500 MHz (δ_H)	Synthetic palmerolide C d_3-MeCN 800 MHz HSQC (δ_C)
1	-	166.20*
2	5.71 d (15.7)	123.26
3	6.84-6.78 m	142.43
4a	2.18-2.12 m	32.43
4b	2.45-2.37 m	
5a	2.18-2.12 m	30.75
5b	2.33-2.24 m	
6	5.49-5.46 m	132.6
7	5.36 dd (15.2, 8.0)	130.08
8	3.75-3.70 m	74.18
9	3.47-3.43 m	75.98
10	4.52 dt (10.4, 3.1)	75.26
11a	1.43-1.36 m	26.09
11b	1.54-1.45 m	
12a	1.43-1.10 m	24.85
13	1.93-1.84 m	31.83*
14	5.46-5.42 m	133.24
15	6.20 dd (14.7, 10.9)	127.95
16	5.76 d (10.7)	128.6
17	-	132.52*
18a	2.20 dd (14.2, 11.1)	43.15
18b	2.33-2.24 m	
19	4.94 ddd (10.5, 7.7, 2.4)	75.26
20	2.78 dt (9.85, 6.92)	37.81
21	5.20 d (9.7)	130.94
22	-	130.26*
23	5.87 d (14.6)	117.18
24	6.93 dd (14.5, 10.5)	122.33
8-OH	3.05 s	-
9-OH	3.26 s	-
17-CH_3	1.64 s	12.88
20-CH_3	0.95 d (6.7)	17.36
22-CH_3	1.76 d (1.2)	16.16
$CONH_2$	5.18-5.09 m	164.23*
CONH	8.16 d (10.6)	163.4*
2’	5.63 s	118.13
3’	-	154.09*
4’	2.16 d (1.1)	19.76
5’	1.86 d (1.1)	27.25

* data from HMBC experiment.

Table 5.4.1 ^{1}H and ^{13}C NMR of synthetic palmerolide C 3b

At this point, with analytical confirmation of the synthesised product in hand we attempted to obtain the NMR spectra in dimethylsulfoxide for a direct comparison with data reported for the natural palmerolide C.[4,10] The obtained ^{1}H NMR spectrum made the comparison possible however, it showed significant differences in signal shifts (Figure 5.4.1, Table 5.4.2). It appeared difficult to unambiguously justify exact correlation of the H8 and H9 signals as the presence of significant amount of water obscured these resonances in the spectra for the synthetic material, but it was clear that they did not match the corresponding signals in the spectra for the natural sample.

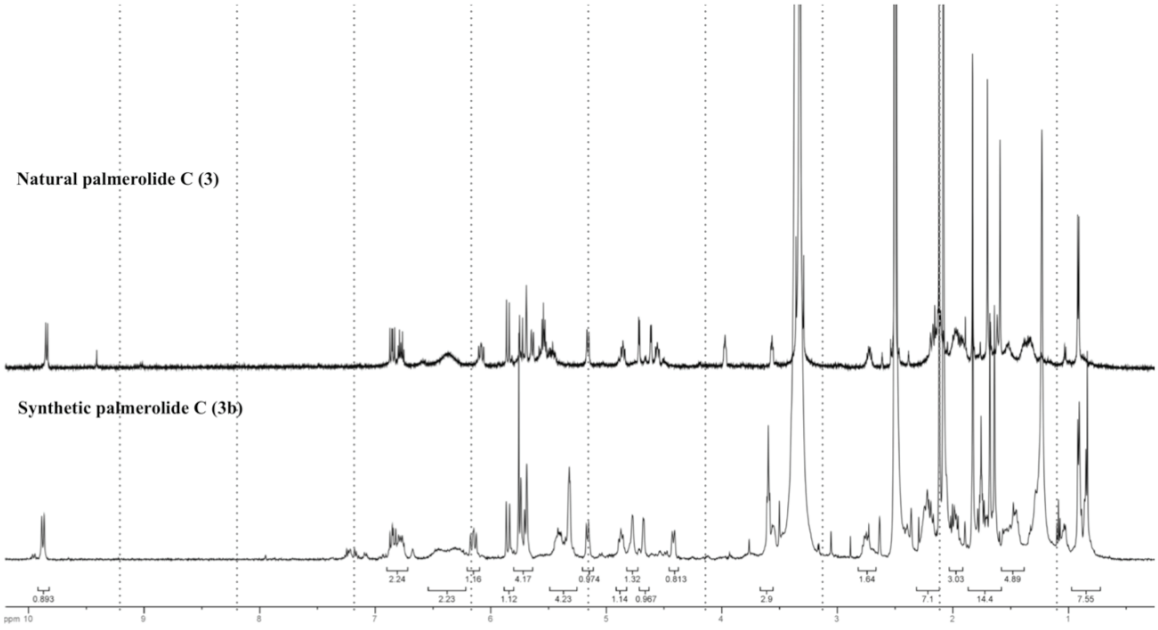


Figure 5.4.1 Comparison of the natural and synthetic palmerolide C ^{1}H NMR in d_6-DMSO

Proton No.	Natural palmerolide C 3 d_6-DMSO 600 MHz (δ_H)	Natural palmerolide C 3 d_6-DMSO 125 MHz (δ_C)	Synthetic palmerolide C 3b d_6-DMSO 500 MHz (δ_H)
1	-	lactone 166.9	-
2	5.73 d (15.5)	122.0	5.76-569 m
3	6.77 ddd (15.4, 7.5, 7.4)	149.8	6.78 dt (15.6, 7.4)
4a	1.30 m	31.7	2.08-1.93 m
4b	2.13 m		
5a	1.89 m	32.2	2.26-2.22 m
5b	1.98 m		2.03-1.97 m
6	5.54 m	131.8	5.46-5.35 m
7	5.58 m	131.1	5.35-5.27 m
8	3.96 m	72.8	3.56 m_{obs}
9	3.56 m	75.6	3.46 m_{obs}
10	4.56 ddd (10.5, 7.5, 3.0)	74.2	4.42 d (10.3)
11a	1.30 m	28.7	1.57-1.50 m
11b	1.49 m		1.49-1.42 m
12	1.95 m	30.1	2.21 m
13	1.99-1.90 m	30.1	1.82-1.78 m
14	5.46 ddd (15.0, 10.0, 5.0)	132.3	5.44-5.40 m
15	6.08 dd (15.0, 12.0)	127.2	6.15 dd (14.1, 11.3)
16	5.63 d (11.0)	128.8	5.76-5.69
17	-	132.5	-
18a	2.07 m	44.1	2.25-2.21 m
18b	2.18 m		2.19-2.15 m
19	4.85 ddd (10.5, 7.8, 2.8)	74.7	4.87 t (8.5)
20	2.70 qdd (9.8, 6.7, 6.7)	37.4	2.75 m
21	5.15 d (9.5)	130.5	5.16 d (9.5)
22	-	133.3	-
23	5.85 d (14.5)	117.2	5.85 d (14.5)
24	6.85 dd (14.6, 9.0)	122.8	6.85 dd (14.0, 10.4)
8-OH	4.62 d (5.0)	-	4.68 br s
9-OH	4.72 d (4.5)	-	4.77 br s
17-CH_3	1.59 s	13.3	1.64 s
20-CH_3	0.90 d (7.0)	17.8	0.91 d (6.5)
22-CH_3	1.69 s	16.5	1.68 s
NH_2	6.37 br	157.6	6.48-6.28 m
NH	9.85 d (10.0)	164.0	9.88 d (10.3)
2’	5.68 s	118.8	5.69-5.76 m
3’	-	152.5	-
4’	1.82 s	27.4	1.83 s
5’	2.11 s	20.3	2.12 s

Table 5.4.2 ^{1}H and ^{13}C NMR data shifts for natural and synthetic palmerolide C.

Our efforts to recover the synthetic sample from dimethylsulfoxide culminated in only small fraction of the initial material being retrieved. However, successful re-isolation of the natural palmerolide C allowed Baker and co-workers to carry out NMR analysis in acetonitrile and allowed direct comparison of the ^{1}H NMR spectra of the synthetic **3b** and natural sample of palmerolide C **3** (Figure 5.4.2).

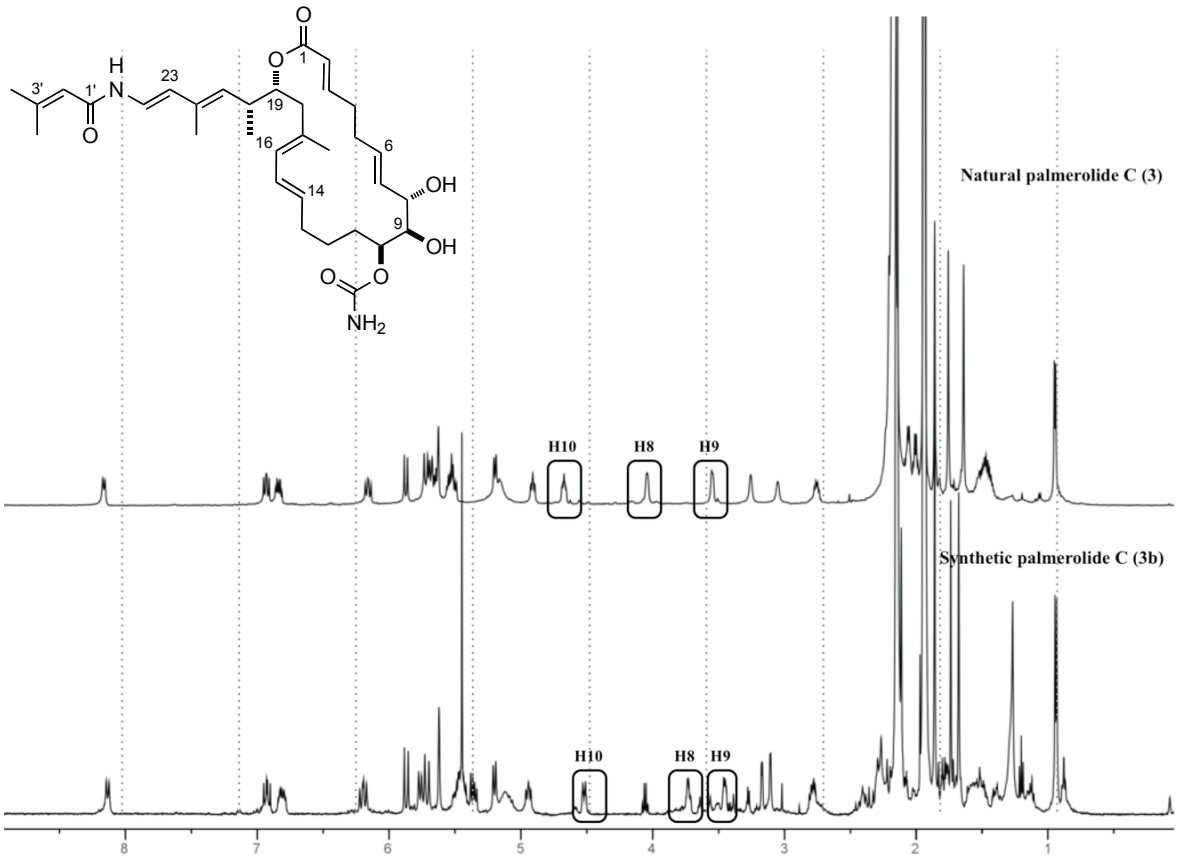


Figure 5.4.2 Comparison of the natural and synthetic palmerolide C ^{1}H NMR in d_3-MeCN.

The observed differences in chemical shift correspond to the signals from the macrocyclic part of the molecule. The highlighted resonances for the H8-H10 stereocentres, despite following a similar splitting pattern in the natural and synthetic spectra, do not match. On a closer inspection (Figure 5.4.3) the H2-H3 and H6-H7 methine protons appeared to be significantly shifted upfield. Signals corresponding to the H14 and H16 protons were identified at different δ_H in both natural and synthetic spectra. The discrepancy in chemical shifts of the crucial resonances indicates that the proposed stereochemical assignment of the natural palmerolide C was incorrect.

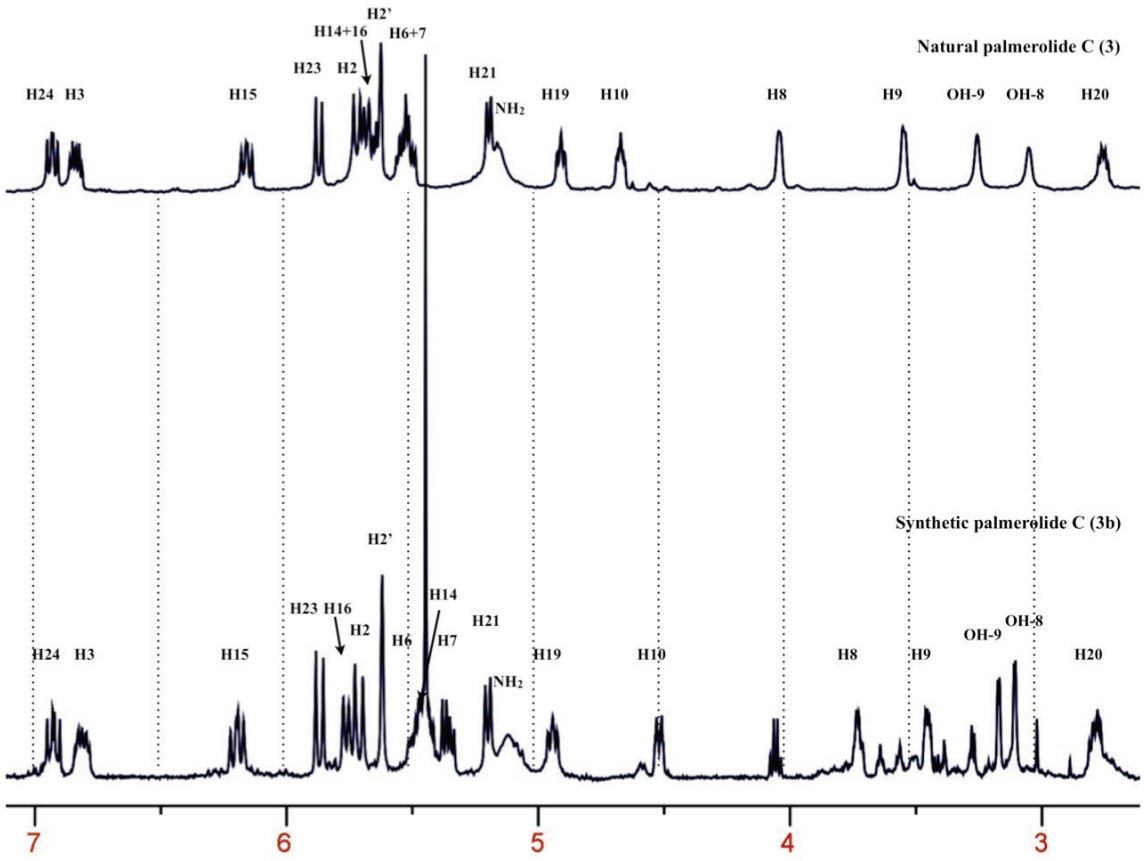


Figure 5.4.3 Comparison of the natural and synthetic palmerolide C ^{1}H NMR in d_3-MeCN.

5.5 Final stereochemical assignment

Our re-examination of the experimental data for the Murata *J*-based analysis of the C8-C10 triad of the natural palmerolide C (**3**) revealed an error (Figure 5.5.1).[21] The Baker group had misinterpreted the Newman projection of the *J*-coupling based analysis, suggesting the arrangement of the C8-C9 stereocentres to be *syn* (Figure 5.5.1, A) and the C9-C10 centres *anti* (Figure 5.5.1, B). Our interpretation indicated that the C8-C9 chiral centres were in fact in an *anti* relationship, while the arrangement of the C9-C10 stereocentres remained *anti* as assigned by Baker (Figure 5.5.1).

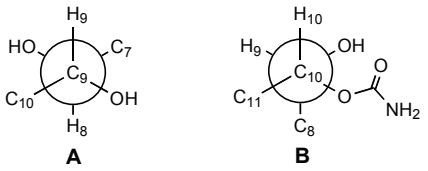


Figure 5.5.1 Newman projections of palmerolide C, reported by Baker group.[10]

This misinterpretation of the stereochemical assignment of the C8-C10 centres had a consequence in the synthesis of diastereoisomer **3b** presented in Figure 5.5.2 with the C8-C9 *syn* and C9-C10 *anti* configuration. As an outcome of our synthetic investigation and final data evaluation we propose the structure **3** shown in Figure 5.5.2 with revised C8-C9 *anti* and C9-C10 *anti* stereocentres to be the absolute configuration of the natural palmerolide C.

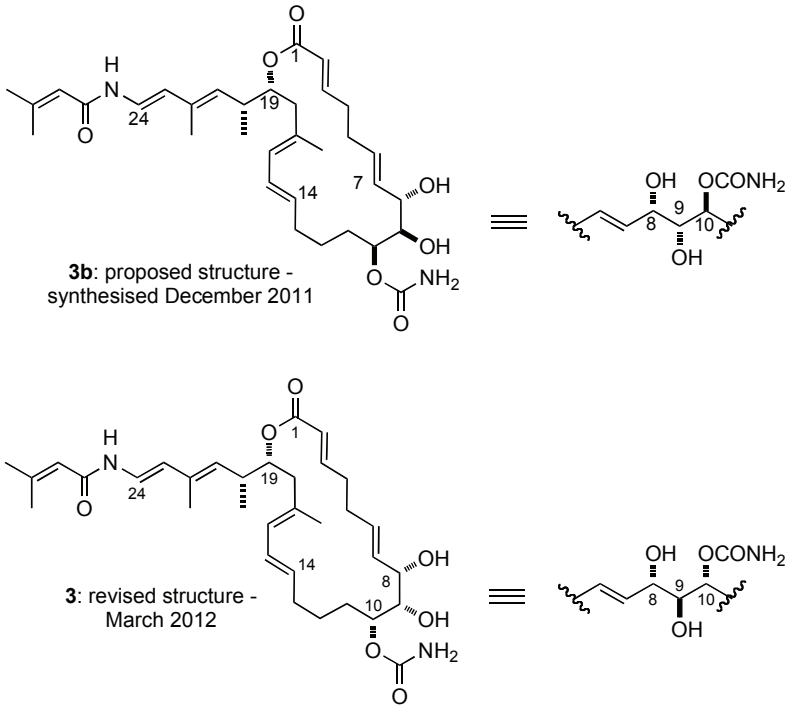


Figure 5.5.2 Proposed and revised structures of palmerolide C.

5.6 Summary

In summary, the first stereochemical assignment turned out to be incorrect due to the mistaken interpretation of the Mosher esters analysis of the C8 stereocentre. The error was related to the different priority of the Mosher acid and Mosher acid chloride substituents consequently affecting the entire resolution of the adjacent C8-C10 centres.

The second assignment was shown to be incorrect due to the misinterpretation of the Newman projection for *J*-based configurational analysis. The first total synthesis of palmerolide C **3b** helped to assign the relative and absolute configuration of this remarkedly interesting natural product (Figure 5.6.1).

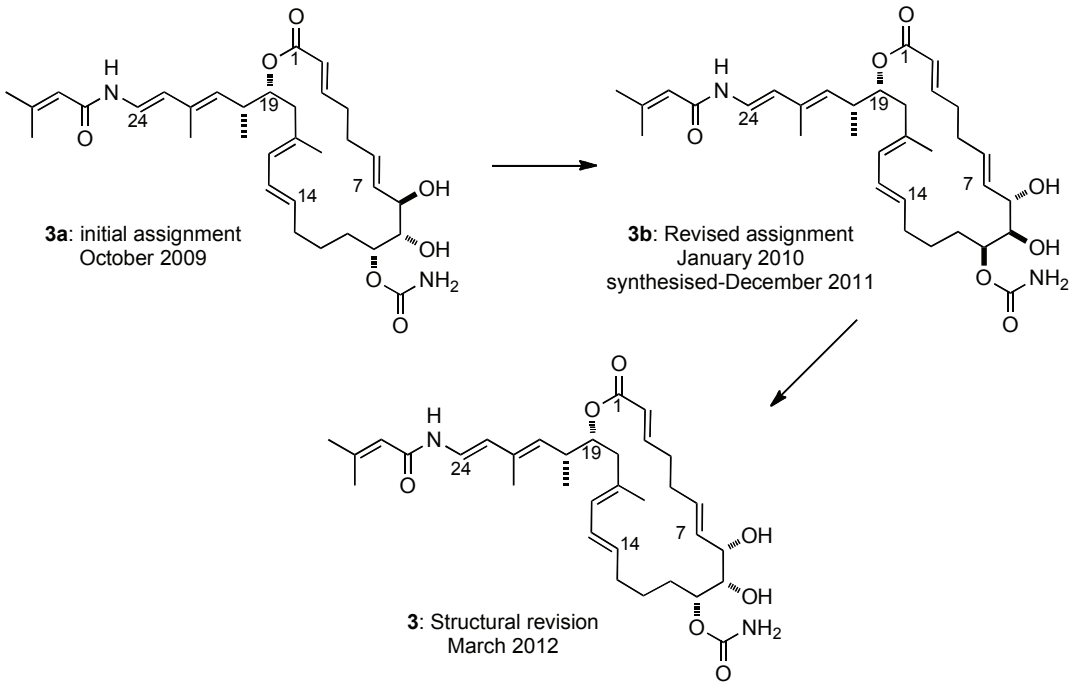


Figure 5.6.1 Summary of the stereochemical outcome.

Chapter 6

6.1 Summary and future work

The first total synthesis of palmerolide C **3b** has been accomplished in an efficient and highly convergent manner. Our synthetic strategy evolved significantly during the venture. The first part of the project aimed at the resolution of the putative stereochemistry of the adjacent C8-C10 stereocentres of the natural product **3**, culminated in the synthesis of the four possible diastereoisomers of C7-C14 degradation fragment. The obtained data set was sent for comparison studies with the natural C7-C14 degradation fragment to the Baker group at the University of South Florida, US. The outcome of their investigation and comparison studies are yet to be concluded.

The original synthetic approach towards the structure with Baker's first stereochemical assignment featured a cross metathesis coupling to assemble the C1-C14 fragment **110** and the Yamamoto vinylogous aldol reaction to advance the construction of the C15-C24 subunit **171**. After making significant progress along these routes, lack of success in the attempted cross-metathesis and Yamamoto vinylogous aldol reactions forced the investigation of alternative synthetic plans. A revised synthetic strategy incorporated the secondary stereochemical assignment of the C8-C10 stereotriad, followed by aldol/elimination sequence to construct the C1-C14 fragment **169**. At this time the vinylogous Mukaiyama aldol reaction was employed to form the C18-C19 bond.

After the successful elaboration of the key subunits, the critical Julia-Kocienski olefination to assemble the *(E,E)*-diene motif provided direct access to the advanced C1-C24 intermediate **210** comprising the entire carbon backbone of palmerolide C with all of the stereocentres already incorporated. Selective deprotection, mild saponification and macrolactonisation under Yamaguchi conditions completed the formation of the 20-membered macrolactone. Cleavage of the silyl groups set the stage for the Buchwald Cu (I)-catalysed enamide formation under stoichiometric conditions. In total the synthesis of

3b contains forty-one steps from commercially available materials with a longest linear sequence of twenty-three steps, starting from the proline-catalysed aldol reaction. The total synthesis of unnatural palmerolide C **3b** was completed with 0.4% overall yield.

With the stereochemical assignment of the C8-C10 stereotriad and completion of the total synthesis of the diastereoisomer of palmerolide C **3b**, the two major goals of this project have been accomplished. In addition, the convergent synthetic route provided a working platform for the synthesis of the other members of the palmerolide family (Figure 6.1.1).

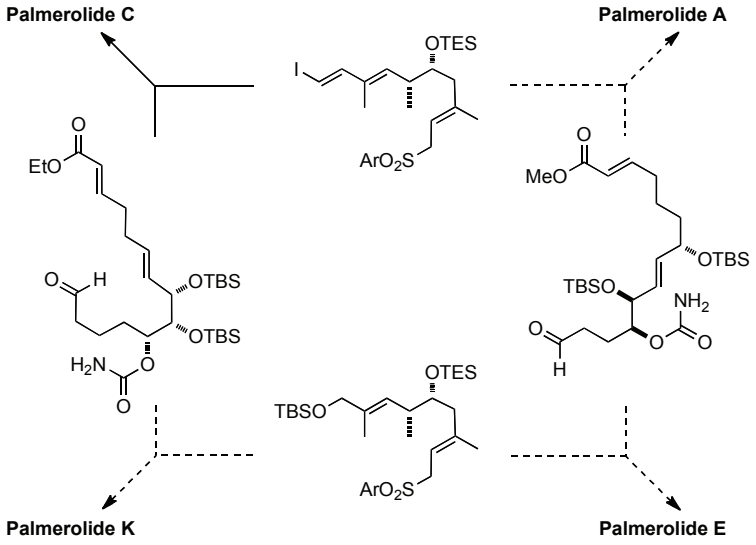
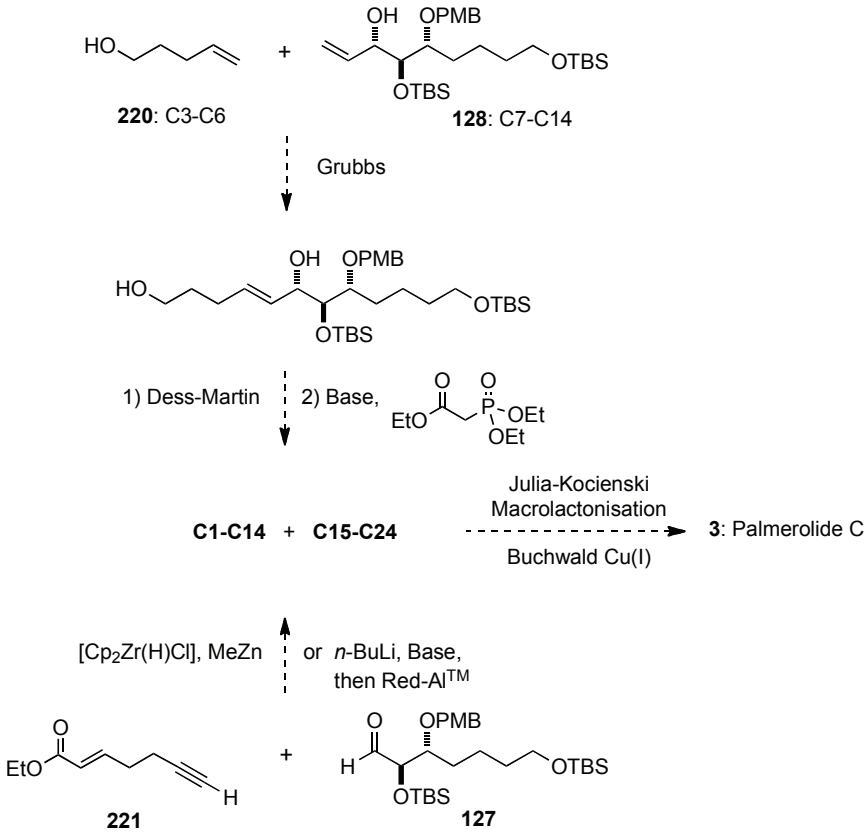


Figure 6.1.1 Synthesis of palmerolides from common intermediates.

However, there are areas of our research on palmerolide C that could warrant further attention. First, the synthesis of palmerolide C **3** with a revised stereochemistry of the C8-C10 stereotriad could be readily accomplished. Although, a synthetic route towards the C7-C14 subunit **128** with the natural product configuration has been developed, the coupling of the C3-C6 **220** and C7-C14 **128** fragments would require attention. The possibility of utilising the cross-metathesis approach could be revisited using C3-C6 subunit **220** followed by incorporation of the C1-C3 enone after the coupling reaction to form C1-C14 subunit. Alternative plan would rely on the Zr-mediated coupling utilising Schwartz reagent and dimethylzinc to introduce C6-C7 alkene. Other possibility to form C6-C7 junction would be the addition of the lithium anion of C1-C7 alkyne **221** to aldehyde **127**. Further exploration of the established synthetic route would provide access to the natural palmerolide C **3**.



Scheme 6.1.1 Alternative route to C1-C14 fragment.

Secondly, our synthesis of C15-C24 subunit **171** could be modified to provide access to the non-iodinated fragment of the palmerolide E and K. Finally, in a broader investigation, this strategy could be used for the synthesis of the other members of the palmerolide family and their derivatives, leading to a library of potential anticancer agents with unique biological properties and selective efficacy against human melanoma cancers.

Chapter 7

7.1 General comments

All reactions were performed in flame-dried glassware under positive pressure of Ar with magnetic stirring unless otherwise stated.

^{1}H NMR spectra were recorded on a Bruker Avance 300 (300 MHz) instrument, Bruker Avance II 400 (400 MHz) instrument or Bruker Avance 500 (500 MHz) instrument, using $CDCl_3$ (or other indicated solvent) as reference and internal deuterium lock. The chemical shift data for each signal are given as δ in units of parts per million (ppm) relative to tetramethylsilane (TMS) where δ_{TMS} = 0.00 ppm. The multiplicity of each signal is indicated by: s (singlet); br s (broad singlet); d (doublet); t (triplet); q (quartet); qn (quintet); sp (septet) or m (multiplet). The number of protons (n) for a given resonance is indicated by nH. Coupling constants (*J*) are quoted in Hz and are recorded to the nearest 0.1 Hz.

^{13}C NMR spectra were recorded on a Bruker Avance 300 (75 MHz) instrument, Bruker Avance II 400 (100 MHz) instrument or Bruker Avance 500 (125 MHz) instrument using the PENDANT sequence and internal deuterium lock. The chemical shift data for each signal are given as δ in units of ppm relative to TMS where δ_{TMS} = 0.00 ppm.

^{19}F NMR spectra were recorded on a Bruker Avance 500 (500 MHz) instrument. Resonances were assigned according to chemical shift, multiplicity, and reference to the literature.

HRMS and LRMS (High and Low resolution mass spectrometry) were recorded using a

Thermofisher LTQ Orbitrap XL mass spectrometer, Finnigan MAT 900 XLT mass spectrometer, Micromass Quattro II mass spectrometer, Waters ZQ4000 mass spectrometer or a Thermofisher DSQ-II mass spectrometer by EPSRC national mass spectrometry service (Swansea, UK) using Electron Impact (EI), Electrospray Ionisation (ES), Chemical Ionisation (CI), Fast Atom Bombardment (FAB), Atmospheric Pressure Chemical Ionisation (APCI) or Atmospheric solids analysis probe (ASAP) techniques. Other spectra were recorded on a Micromass LCT mass spectrometer by the University of St Andrews mass spectrometry service (School of Chemistry and Biomolecular Sciences). The parent ion (M^+, $[M+H]^+$, $[M-H]^+$, $[M+Na]^+$ or $[M+NH_4]^+$) is quoted.

IR spectra were recorded on a Perkin-Elmer Paragon Series 1000 FTIR spectrometer as thin films between sodium chloride discs or PTFE thin films as indicated. Absorption maxima are reported in wavenumbers (cm^{-1}). Intensities of the maxima are quoted as strong (s), medium (m) or weak (w).

Optical rotations were measured using an Perkin-Elmer Model 341 automatic polarimeter, in cells with a path length of 1 dm. The concentration (c) is expressed in g/100 mL (equivalent to g/0.1 dm^3). Specific rotations are denoted $[\alpha]_D^T$ and are given in implied units of 10^{-1} deg cm^2g^{-1}, where T is temperature in °C.

X-ray analysis of single crystals was conducted by Prof. Alexandra Slawin at the University of St Andrews on a Rigaku Cu MM007 high brilliance generator with Saturn 92 CCD and XStream LT accessories.

Analytical thin layer chromatography (TLC) was carried out on pre-coated 0.25 mm Merck Kieselgel 60 F_{254} plates. Visualisation was by absorption of UV light, or thermal development after dipping in either an aqueous solution of potassium permanganate, potassium carbonate and sodium hydroxide, an ethanolic solution of phosphomolybdic acid (PMA) or a solution of ninhydrin in butan-2-ol.

Flash column chromatography was carried out on silica gel 60 (E. Merck, 40-63 micron) or on activated aluminium oxide (Acros, 50-200 micron, neutral) as indicated, under a positive pressure of compressed air.

Kugelrohr bulb-to-bulb distillations were carried out using a Büchi Glass Oven B-585 machine. Boiling points are the actual oven temperatures.

Reagents and solvents were purified by standard means. Methanol was distilled from CaH_2 in a recycling still under nitrogen. Dichloromethane (CH_2Cl_2), toluene, tetrahydrofuran (THF) and diethyl ether (Et_2O) were dried by passage through two columns of alumina using a MBRAUN SPS-800 solvent purification system under Ar. Anhydrous *N*,*N'*-dimethylformamide (DMF) was purchased from Aldrich UK and dried by distillation from 4Å molecular sieves under Ar atmosphere. Chloroform was passed through alumina column and dried by distillation from 4Å molecular sieves under Ar atmosphere. Triethyl amine (Et_3N), BF_3•Et_2O and 2,6-lutidine were distilled from CaH_2 under Ar. An L-erythrulose hydrate solution was desiccated according to the published procedure. Dowex 50 resin was washed with water, 3M HCl and methanol prior to use. Chemicals were purchased from Acros UK, Aldrich UK, Avocado UK, Fisher UK or Fluka UK. All reagents and solvents were purified and dried, where necessary, by standard techniques. Where appropriate and if not stated otherwise, all non- aqueous reactions were performed under an inert atmosphere of argon, using a vacuum manifold with the gas passed through 4Å molecular sieves and self-indicating silica gel. Under reduced pressure refers to the use of a rotary evaporator attached to a diaphragm pump. Hexane refers to a mixture of hexanes and petroleum ether to the fraction boiling between 40-60 ºC. Room temperature (rt) refers to the temperature of approximately 25 °C.

Miscellaneous, brine refers to a saturated solution of sodium chloride in deionised water. Reactions at -78 ºC were readily achieved with isopropanol and dry ice in a Dewar vacuum flask, -100 ºC was achieved with CH_3OH and liquid nitrogen.

7.2 Preparation of reagents

Zinc borohydride ($Zn(BH_4)_2$)[128,129]

To a round bottom flask equipped with magnetic bar at rt was added anhydrous $ZnCl_2$ (8.04 g, 58.9 mmol), $NaBH_4$ (5.12 g, 135 mmol) and THF (118 mL). The reaction mixture was stirred for 24 h to afford the clear solution *c*. 0.5 M which is stable over a period of 6 months when stored under argon at room temperature.

Thexyl borane ($thexylBH_2$)[66]

To a round bottom flask equipped with magnetic bar at 0 ºC was added BH_3•THF (10 mL, 1M soln. in THF) and 2,3-dimethyl-2-butene (10 mL, 1M soln. in THF) was then added dropwise over 30 min. The reaction mixture was stirred for 1h to afford the clear solution *c*. 0.5M which is stable for a week when stored under argon in the fridge.

Dicyclohexylboron chloride (*c*-Hex_2BCl)[130]

To a stirred solution of cyclohexene (20.0 mL, 197 mmol, distilled from CaH_2) in Et_2O (120 mL) at -10 ºC was added monochloroborane•dimethylsulfide (10.3 mL, 98.6 mmol). The mildly exothermic reaction was controlled by the rate of addition. The resulting solution was stirred at 0 ºC for 1 h. The solvent and volatiles were removed by distillation at atmospheric pressure and the product purified by distillation under reduced pressure to afford the title compound as a colourless oil (16.0 g, 76%); **B.pt**. 105-110 ºC at 0.5 mmHg. Lit. 104-105 ºC/0.5 mmHg.

Lithium methoxyborohydride ($LiBH_3(OMe)$)[71-73]

To a lithium borohydride solution (0.5 mL, 2M soln. in THF, 1.0 mmol) in THF (4.5 mL) at 0 ºC was added MeOH (40.5 µL, 1.0 mmol). Stirring was continued for 1.5 h at rt to provide a colourless solution *c.* 0.2M which could be stored for 48 h under argon.

Dicyclohexylboron chloride•Triethyamine complex (*c*-Hex_2BCl•NEt_3)[71-73]

To a stirred solution of dicyclohexylboron chloride (120 µL, 0.58 mmol) in THF (3 mL) at 0 ºC was added Et_3N (75 µL, 1.02 mmol) to provide a colourless solution *c*. 0.19M which was used immediately in 1,3-*syn* reduction.

_p_–Methoxybenzyl trichloroacetimidate (PMBTCA)[86]

To a solution of *p*-methoxybenzyl alcohol (14.0 mL, 15.6 g, 113 mmol) in CH_2Cl_2 (100 mL) at -10 ºC was added aqueous solution of KOH (100 g/100 mL) and tetrabutylammonium hydrogen sulfate (384 mg, 1.13 mmol) followed by dropwise addition of trichloroacetonitrile (12.5 mL, 18.0 g, 125 mmol). The reaction mixture was then allowed to warmed to rt over 2 h and the layers were separated, the aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL), the combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by distillation afforded the title compound (28.0 g, 88%) as a colourless solution. **B.pt.** 120-145 ºC at 0.5 mmHg. Lit. 135 ºC at 0.7 mmHg.[86] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.38 (2H, d, *J* = 8.8 Hz, Ar-H), 6.91 (2H, d, *J* = 8.8 Hz, Ar-H), 5.28 (2H, s, CH_2), 3.81 (3H, s, OCH_3).

1-Hydroxy-1,2-benziodoxol-3(1H)-one 1-Oxide (IBX)[110]

To a solution of Oxone (83.0 g, 0.135 mol) in deionized water (225 mL, 0.45 M) at rt was added 2-iodobenzoic acid (25.0 g, 0.10 mol). The reaction mixture was warmed to 70-73 °C over 20 min and mechanically stirred at this temperature for 3 h. The suspension was then cooled to 5 °C and left at this temperature for 1.5 h with slow stirring. The mixture was filtered and the solid was repeatedly rinsed with water (6 × 50 mL) and acetone (2 × 50 mL). The white, crystalline solid (24.0 g, 86%) was left to dry at rt for 16 h.

1,1,1-Triacetoxy-1,1-dihyd-1,2-benziodoxol-3(1*H*)-one (Dess-Martin reagent)[111]

To a solution of acetic anhydride (82.0 mL, 88.7 g, 869 mmol) and TsOH•H_2O (120 mg, 0.631 mmol) at rt was added IBX (24.0 g, 85.7 mmol) and the reaction mixture equipped with a drying tube was heated at 80 ºC for 2h. The mixture was then cooled in ice-water bath and the suspension was filtered and washed with Et_2O (5 × 20 mL). The resulting white, crystalline solid (30.0 g, 83%) was quickly transferred to an argon flushed amber-glass bottle and stored at -25 ºC.

(1-Methoxy-3-methylbuta-1,3-dienyloxy)-trimethylsilane (173)[131]

To a stirred solution of diisopropylamine (8.41 mL, 60.0 mmol) in THF (50 mL) at 0 ºC was added n-BuLi (32.5 mL, 1.6 M soln. in hexane, 52.5 mmol) and the reaction mixture was stirred at 0 ºC for 15 min before cooling to -78 ºC. Methyl 3,3-dimethylacrylate (6.54 mL, 50.0 mmol) was then added. After 1h trimethylsilyl chloride (7.61 mL, 60.0 mmol) was added as a solution in THF (5 mL) and the reaction mixture was warmed to 0 ºC and stirring continued for 1h. The reaction mixture was concentrated under reduced pressure to a volume of 20 mL and pentane (100 mL) was added. The suspension was filtered through celite and concentrated under reduced pressure. The residue was distilled under vacuum (bp 48 ºC at 0.75 mmHg) to give the silyl enol ether **173** as a colourless oil (7.32 g, 79%).

^{1}H NMR (400 MHz; $CDCl_3$) δ 4.78 (1H, dt, *J* = 2.7, 0.7 Hz, H-4a), 4.54 (1H, dq, *J* = 2.7, 1.4 H-4b), 4.26 (1H, s, H-2), 3.57 (3H, s, OC$\underline{H}_3$), 1.93 (3H, dd, *J* = 1.4, 0.7 Hz, C$\underline{H}_3$), 0.23 (9H, s, Si-(C$\underline{H}_3$)$_3$).

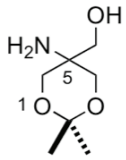
3-Methyl but-2-enamide (218).[132]

To a suspension of 3,3-dimethylacrylic acid (5.0 g, 50 mmol) in CH_2Cl_2 (100 mL) at 0 ºC was added a catalytic amount of DMF (60 µL) and oxalyl chloride (4.7 mL, 55 mmol). The resulting reaction mixture was stirred at 0 ºC for 15 min and then at rt for a further 90 min. CH_2Cl_2 (100 mL) at -78 ºC, which had been saturated with ammonia gas for 20 min, was then cannulated into the cooled to -78 ºC reaction mixture. After stirring for an additional 20 min, the reaction mixture was quenched with water (100 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure to give 3-methyl but-2-enamide **218** (2.8 g, 57%) as white crystals, which could be used without any further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 (1H, br s, N$\underline{H}_2$), 5.61 (1H, dt, *J* = 2.7, 1.3 Hz, H-2), 5.51 (1H, br s, N$\underline{H}_2$), 2.12 (3H, d, *J* = 1.3 Hz, H-4), 1.83 (3H, d, *J* = 1.4 Hz, C$\underline{H}_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.3, 152.6, 117.7, 27.3, 19.9.

7.3 Experimental procedures for Chapter 2

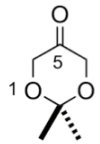
2,2-Dimethyl-5-amino-5-hydroxymethyl-1,3-dioxane (71)[51]



Trizma® base (50 g, 0.30 mol), 2,2-dimethoxypropane (40 g, 0.40 mol), CSA (2.6 g, 11 mmol) in dimethylformamide (100 mL) were stirred at rt for 24 h. After addition of Et_3N (2.5 mL, 18 mmol) the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (700 mL) followed by addition of Et_3N (40 mL, 0.30 mol) and stirring was continued for 15 min. The precipitate was filtered and washed with EtOAc. The filtrate was evaporated to afford 2,2-dimethyl-5-amino-5-hydroxymethyl-1,3-dioxane **71** (37.1 g, 90%) as a colourless solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.82 (2H, d, J = 11.8 Hz, H-4a, H-6a), 3.62 (2H, d, J = 11.8 Hz, H-4b, H-6b), 3.56 (2H, s, H-7), 3.48 (3H, s, O$\underline{H}$, N$\underline{H_2}$), 1.45 (3H, s, C2-C$\underline{H_3}$), 1.42 (3H, s, C2-C$\underline{H_3}$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 98.4, 66.7, 64.2, 50.6, 25.0, 22.1.

2,2-Dimethyl-1,3-dioxan-5-one (dioxanone) (63)[51]

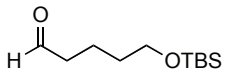


To a solution of **48** (20.0 g, 12.4 mmol) and KH_2PO_4 (16.9 g, 12.4 mmol) in water (200 mL) at 5 °C was added $NaIO_4$ (370 mL, 0.5 M soln. in H_2O, 18.5 mmol) dropwise over 2 h, while the temperature was maintained at 5-10 °C. After 12 h at rt, CH_2Cl_2 (200 mL) was then added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (10 × 30 mL), the combined extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by distillation (bp. 25°C/1 torr) afforded 2,2-dimethyl-1,3-

dioxan-5-one **63** (9.68 g, 60%) as a colourless oil.

R_f 0.51 (10% EtOAc/Hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.16 (4H, s, H-4, H-6) and 1.46 (6H, s, C2-C$\underline{H}_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 208.0, 100.1, 66.8, 23.5.

5-(*tert*-Butyldimethylsilyloxy)pentanal (69)[133]



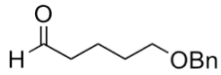
To a solution of 1,4-butanediol **23** (6.06 mL, 60.5 mmol), Et_3N (3.66 mL, 26.3 mmol) and DMAP (246 mg, 2.00 mmol) in CH_2Cl_2 (30.0 mL) at rt was slowly added a solution of TBSCl (3.04 g, 20.1 mmol) in CH_2Cl_2 (10.0 mL). After 16 h, the reaction mixture was poured onto brine (30 mL) and layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic extracts were washed with water (50.0 mL), brine (50 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by flash column chromatography (5% EtOAc/Hexanes) provided alcohol **73** (11.1 g, 85%) as a colourless oil.

R_f 0.48 (50% EtOAc/Hexanes); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.66-3.60 (4H, m, H-1, 5), 1.65-1.52 (4H, m, H-2, 4), 1.45-1.35 (2H, m, H-3), 0.90 (9H, s, Si-C(C$\underline{H}_3$)$_3$), 0.05 (6H, m, Si-(C$\underline{H}_3$)$_2$).

To a solution of oxalyl chloride (0.92 mL, 11.0 mmol) in CH_2Cl_2 (20.0 mL) at -78 ºC was slowly added DMSO (1.75 mL, 24.1 mmol). After 30 min, a solution of alcohol **73** (2.18 g, 10.1 mmol) in CH_2Cl_2 (20.0 mL) was added, dropwise. After 1 h, Et_3N (19.1 mL, 137 mmol) was added and the slurry was allowed to attain rt. After 1 h, saturated NH_4Cl (20 mL) solution was added and layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 40 mL) and the combined organic extracts were washed with H_2O (30 mL), brine (30 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude aldehyde **69** (1.73 g, 80%) was used without further purification.

R_f 0.75 (25% EtOAc/Hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.7 (1H, t, *J* = 1.7 Hz, H-1), 3.63 (2H, t, *J* = 6.2 Hz, H-5), 2.46 (2H, td, *J* = 7.29, 1.76 Hz, H-2), 1.66-1.75 (2H, m, H-3), 1.50-1.59 (2H, m, H-4), 0.89 (9H, s, Si-C(C$\underline{H}_3$)$_3$), 0.05 (6H, s, Si-(C$\underline{H}_3$)$_2$).

5-(Benzyloxy)pentan-1-al (76)[134]



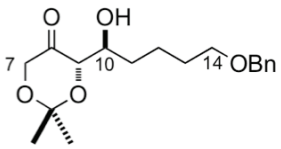
To a solution of pentane-1,5-diol (6.70 mL, 64.0 mmol) in THF (100 mL) at 0 ºC was added NaH (1.30 g, 54.0 mmol). The reaction mixture was stirred at 0 ^{o}C and benzyl bromide (4.60 mL, 34.0 mmol) in THF (20 mL) was added *via* cannula. After 12 h at rt, MeOH (10 mL) was added and the reaction mixture was concentrated under reduced pressure to the *ca*. 50 mL volume. The residue was extracted with CH_2Cl_2 (3 × 20 mL), washed with brine (50 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by flash column chromatography (20-40% EtOAc/Hexanes) afforded product **77** (4.1 g, 66%) as a colourless oil.

***R**f* 0.31 (20% EtOAc/Hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.30-7.19 (5H, m, Ar-H), 4.43 (2H, s, OC$\underline{H}_2$Ph), 3.53 (2H, t, *J* = 6.52 Hz, H-5), 3.41 (2H, t, *J* = 6.49 Hz, H-1), 1.88 (1H, bs, O$\underline{H}$), 1.61-1.54 (2H, m, H-3), 1.53-1.46 (2H, m, H-2), 1.41-1.33 (2H, m, H-4).

To a solution of oxalyl chloride (1.44 mL, 17.0 mmol) in CH_2Cl_2 (10.0 mL) at -78 ºC was added a solution of DMSO (2.64 mL, 34.0 mmol) dropwise. The reaction mixture was stirred at -78 ºC for 15 min and a solution of alcohol **77** (3.00 g, 15.5 mmol) in CH_2Cl_2 (20.0 mL) was added. The reaction mixture was stirred at -78 ºC for an additional 15 min. and Et_3N (10.8 mL, 77.0 mmol) was then added, and the mixture was allowed to warm to rt. The reaction was quenched by addition of water (30 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with saturated NH_4Cl (50 mL) solution and brine (50 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The resulting oil was purified by flash column chromatography (20% EtOAc/Hexanes) to give **76** (1.90 g, 65%) as a colourless oil.

***R**f* 0.41 (20% EtOAc/Hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.76 (1H, t, *J* = 1.7 Hz, H-1), 7.35-7.27 (5H, m, ArH), 4.49 (2H, s, OC$\underline{H}_2$Ph), 3.48 (2H, t, *J* = 6.1 Hz, H-5), 2.45 (2H, td, *J* = 7.2, 1.7 Hz, H-2), 1.78-1.70 (2H, m, H-3) and 1.65-1.61 (2H, m, H-4).

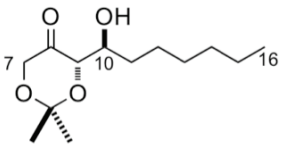
(*S*)-4-((*S*)-5-(Benzyloxy)-1-hydroxypentyl)-2,2-dimethyl-1,3-dioxan-5-one (**78**)



To a solution of dioxanone **63** (1.00 g, 7.69 mmol) in DMF (5.0 mL) at rt was added (*S*)-proline (221 mg, 1.92 mmol). The resulting mixture was stirred for 15 min and aldehyde **76** (880 mg, 7.69 mmol) was added. After 5 days, saturated NH_4Cl (5.0 mL) solution was added and the layers were separated. The aqueous phase was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by flash column chromatography (10% EtOAc/Hexanes) afforded aldol product **78** (237 mg, 23%) as a colourless oil.

R_f 0.21 (10% EtOAc/Hexanes); $[\alpha]_D^{20}$ -16.0 (*c* 0.10, $CHCl_3$); **IR υ_{max}** (thin film/cm^{-1}) 3395, 2912, 1736, 1652, 1392, 1225, 1197, 1067, 911; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.35-7.31 (5H, m, Ar-H), 4.50, (2H, s, OC<u>H</u>$_2$Ph), 4.25 (1H, dd, *J* = 17.3, 1.5 Hz, H-7A), 4.07 (1H, dd, *J* = 6.9, 1.5 Hz, H-9), 4.01 (1H, d, *J* = 17.3 Hz, H-7B), 3.92-3.84 (1H, m, H-10), 3.53-3.44 (2H, t, *J* = 6.4 Hz, H-14), 2.97 (1H, d, *J* = 3.9 Hz, O<u>H</u>), 1.70-1.56 (6H, m, H-11, 12, 13), 1.46 (3H, s, C-C<u>H</u>$_3$), 1.42 (3H, s, C-C<u>H</u>$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): 211.6, 139.0, 128.7, 127.9, 127.8, 101.3, 76.2, 73.2, 70.87, 70.69, 67.1, 32.4, 30.0, 24.2, 23.9, 22.1; **HRMS** (ES^+) calcd. for $C_{18}H_{27}O_5$ $[M+H]^+$ 323.1853, found 323.1857.

(*S*)-4-((*S*)-1-Hydroxypent-4-enyl)-2,2-dimethyl-1,3-dioxan-5-one (**83**)



To the stirred dioxanone **63** (1.00 g, 7.69 mmol) in $CHCl_3$ (5.0 mL) at rt, heptanal **82** (0.88 g, 7.69 mmol) was added. After 5 days, saturated NH_4Cl (5.0 mL) solution was added and the layers were separated. The aqueous phase was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), filtered

and concentrated under reduced pressure. Purification by flash column chromatography (10% EtOAc/Hexanes) afforded aldol product **83** (0.42 g, 45%).

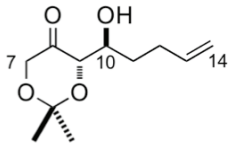
***R*$_f$** 0.38 (10% EtOAc/Hexanes); $[\alpha]_D^{20}$ -12.0 (*c* 0.10, $CHCl_3$); **IR υ_{max}** (thin film/cm^{-1}) 3514, 2948, 2921, 2862, 1739, 1373, 1223, 1094, 860; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 4.25 (1H, dd, *J* = 17.3, 1.5 Hz, H-7A), 4.07 (1H, dd, *J* = 6.9, 1.5 Hz, H-9), 4.01 (1H, d, *J* = 17.3 Hz, H-7B), 3.90-3.85 (1H, m, H-10), 2.95 (1H, d, *J* = 2.6 Hz, O<u>H</u>), 1.55-1.42 (2H, m, H-11), 1.46 (3H, s, C-C<u>H</u>$_3$), 1.43 (3H, s, C-C<u>H</u>$_3$), 1.25-1.19 (8H, m, H-12, H-13, H-14, H-15), 0.84-0.78 (3H, m, H-16); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 211.4, 101.1, 76.1, 70.7, 66.9, 32.4, 31.9, 29.4, 25.1, 24.0, 23.6, 22.7, 14.2; **HRMS** (ES^+) calcd. for $C_{13}H_{28}NO_4$ $[M + NH_4]^+$ 262.2013, found 262.2011.

4-Pentenal (84)[135]

Neat allyl vinyl ether **85** (4.0 g, 47 mmol) sealed in a microwave tube was heated at 160 °C in a microwave reactor (200 W) for 2 h to give aldehyde **84** (3.9 g, 98%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (1H, t, *J* = 1.6 Hz, H-1), 5.83 (1H, ddt, *J* = 17.1, 10.3, 6.6 Hz, H-4), 5.08-4.98 (2H, m, H-5), 2.55-2.50 (2H, m, H-2), 2.41-2.34 (2H, m, H-3).

(*S*)-4-((*S*)-1-Hydroxypent-4-enyl)-2,2-dimethyl-1,3-dioxan-5-one (**86**)

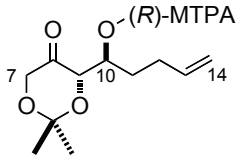


To a solution of dioxanone **63** (1.00 g, 7.69 mmol) in $CHCl_3$ (5.0 mL) at 0 ºC was added (*S*)-proline (221 mg, 1.92 mmol). The resulting mixture was stirred for 15 min and aldehyde **84** (539 mg, 6.41 mmol) was then added. After 5 days, saturated NH_4Cl (5.0 mL) solution was added and the layers were separated. The aqueous phase was extracted with EtOAc (3 × 15 mL) and the combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by flash

column chromatography (10% EtOAc/Hexanes) afforded aldol product **86** (576 mg, 44%) as a colourless oil.

***R**f* 0.26 (10% EtOAc/Hexanes); $[\alpha]_D^{20}$ -4.0 (*c* 0.25, $CHCl_3$); **IR** υ_{max} (thin film/cm^{-1}) 3411, 2922, 1732, 1640, 1375, 1195, 1067, 911; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.82 (1H, ddt, *J* = 17.2, 10.3, 6.8 Hz, H-13), 5.06-4.94 (2H, m, H-14), 4.24 (1H, dd, *J* = 17.4,1.5 Hz, H-7a), 4.08 (1H, dd, *J* = 7.0, 1.5 Hz, H-9), 4.01 (1H, d, *J* = 17.3 Hz, H-7b), 3.93-3.85 (1H, ddt, *J* = 9.1, 6.4, 3.0 Hz, H-10), 2.94-2.89 (1H, d, *J* = 3.9 Hz, OH), 2.34-2.22 (1H, m, H-12a), 2.20-2.08 (1H, m, H-12b), 1.78-1.68 (1H, m, H-11a), 1.64-1.53 (1H, m, H-11b), 1.46 (3H, s, C-CH_3) and 1.42 (3H, s, C-CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 211.3, 138.4, 115.1, 101.1, 76.0, 70.1, 66.8, 31.6, 29.4, 23.9, 23.7; **HRMS** (ES^+) calcd. for $C_{11}H_{18}NaO_4$ $[M+Na]^+$ 237.1097, found 237.1101.

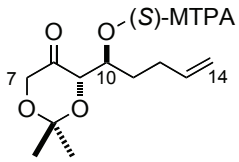
***(R)*-Mosher ester of 86 (87)**



To a stirred mixture of alcohol **86** (10.0 mg, 46.6 μmol), DCC (47.0 mg, 0.232 mmol) and DMAP (11.0 mg, 93.3 μmol) in CH_2Cl_2 (1.0 mL) at rt was added (+)-(*R*)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (23.0 mg, 93.3 μmol) in one portion. After 16 h, the crude reaction mixture was directly purified by flash column chromatography (5% EtOAc/Hexanes) to give (*R*)-MTPA ester **87** (9.0 mg, 45%).

***R**f* 0.56 (10% EtOAc/Hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.63-7.52 (2H, m, Ar-H), 7.48-7.36 (3H, m, Ar-H), 5.81-5.71 (1H, m, H-13), 5.54-5.51 (1H, m, H-10), 5.04-5.01 (1H, m, H-14a), 5.01-4.98 (1H, m, H-14b), 4.43 (1H, dd, *J* = 2.8, 1.5 Hz, H-9), 4.13 (1H, dd, *J* = 16.9, 1.5 Hz, H-7a), 3.93 (1H, d, *J* = 16.8 Hz, H-7b), 3.54 (3H, s, MTPA-OCH_3) 2.11-1.95 (2H, m, H-11), 1.791.63 (2H, m, H-12), 1.37 (3H, s, C-CH_3), 1.31 (3H, s, C-CH_3); **^{19}F NMR** (376 MHz; $CDCl_3$) δ_F -71.27, -71.36, 97% de.

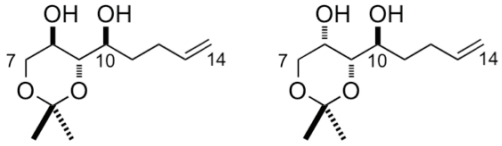
(*S*)-Mosher ester of 86 (88)



To a stirred mixture of alcohol **86** (5.0 mg, 23 μmol), DCC (23.0 mg, 110 μmol) and DMAP (5.0 mg, 46.0 μmol) in CH_2Cl_2 (1.0 mL) at rt was added (+)-(*S*)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (12.0 mg, 46.0 μmol) in one portion. After 16 h, the crude reaction mixture was purified directly by flash column chromatography (5% EtOAc/Hexanes) to give (*S*)-MTPA ester **88** (6.0 mg, 60%).

***R**f* 0.56 (10% EtOAc/Hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.62-7.48 (2H, m, Ar-H), 7.46-7.36 (3H, m, Ar-H), 5.76-5.66 (1H, m, H-13), 5.48 (1H, td, *J* = 6.1, 2.7 Hz, H-10), 4.98 (1H, m, H-14a), 4.94 (1H, m, H-14b), 4.57 (1H, dd, *J* = 3.1, 1.3 Hz, H-9), 4.20 (1H, dd, *J* = 17.0, 1.3 Hz, H-7a), 3.98 (1H, d, *J* = 17.0 Hz, H-7b), 3.60 (3H, s, MTPA-OCH_3), 2.05-1.87 (2H, m, H-11), 1.69-1.57 (2H, m, H-12), 1.45 (3H, s, C-CH_3), 1.42 (3H, s, C-CH_3).

(4*S*,5*R*)-4-((*S*)-1-Hydroxypent-4-en-1-yl)-2,2-dimethyl-1,3-dioxan-5-ol (92),
(4*S*,5*S*)-4-((*S*)-1-Hydroxypent-4-en-1-yl)-2,2-dimethyl-1,3-dioxan-5-ol (93)



Method A

To a solution of aldol adduct **86** (50.0 mg, 0.233 mmol) in MeOH (2.0 mL) at -78 ºC was added $NaBH_4$ (10.0 mg, 0.279 mmol). After 1 h the reaction mixture was quenched with saturated NH_4Cl (5.0 mL) solution and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (10% EtOAc/Hexanes) to give compounds **92** (20.0 mg, 40 %) and **93** (7.0 mg, 14%) as colourless oils.

Method B

To a solution of $Zn(BH_4)_2$ (5.0 mL, 0.5 M in Et_2O, 2.5 mmol) at -78 ºC was added aldol adduct **86** (90.0 mg, 0.47 mmol). After 1 h the reaction mixture was quenched with saturated NH_4Cl (5.0 mL) solution and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc/Hexanes) to give compounds **92** (42.0 mg, 44 %) and **93** (8.0 mg, 10%) as colourless oils.

Method C

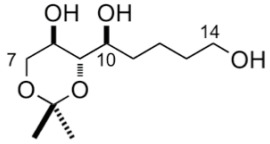
To a solution of aldol adduct **86** (50.0 mg, 0.233 mmol) in CH_3CN (2.0 mL) at -40 ºC was added $Me_4NBH(OAc)_3$ (18.0 mg, 0.689 mmol) and glacial acetic acid (0.2 mL). After 10 h the reaction mixture was warmed up and quenched with saturated $NaHCO_3$ (5.0 mL) solution and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc/Hexanes) to give compounds **92** (14.0 mg, 28 %) and **93** (14.0 mg, 28%) as colourless oils.

92 1,3-*syn*: *R*$_f$ 0.16 (20% EtOAc/Hexanes); $[\alpha]_D^{20}$ -30.7 (*c* 1.8, $CHCl_3$); **IR υ_{max}** (thin film/cm^{-1}) 3398, 2991, 2923, 1444, 1378, 1207, 1067, 914, 863; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.86 (1H, ddt, *J* = 17.1, 10.3, 6.8 Hz, H-13), 5.11-4.98 (2H, m, H-14), 3.88 (1H, dd, *J* = 11.3, 5.4 Hz, H-7a), 3.77 (2H, m, H-8, H-10), 3.61 (1H, dd, *J* = 11.2, 8.5 Hz, H-7b), 3.46 (1H, dd, *J* = 8.7, 7.1 Hz, H-9), 3.32 (1H, br s, C8-O<u>H</u>), 2.49 (1H, br s, C10-O<u>H</u>), 2.12-2.29 (2H, m, H-12), 1.88-1.80 (1H, m, H-11a), 1.58-1.49 (1H, m, H-11b), 1.45 (3H, s, C-C<u>H</u>$_3$), 1.36 (3H, s, C-C<u>H</u>$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 138.6, 115.3, 98.9, 75.4, 75.0, 67.3, 64.3, 32.6, 29.7, 28.3, 19.8; **HRMS** (ES^+) calcd. for $C_{11}H_{20}NaO_4$ $[M+Na]^+$ 239.1254, found 239.1254.

93 1,3-*anti*: *R*$_f$ 0.15 (20% EtOAc/Hexanes); $[\alpha]_D^{20}$ +3.7 (*c* 1.1, $CHCl_3$); **IR υ_{max}** (thin film/cm^{-1}) 3401, 2920, 2873, 1455, 1380, 1332, 1277, 911, 853; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.85 (1H, ddt, *J* = 17.0, 10.3, 6.7 Hz, H-13), 5.09-4.97 (2H, m, H-14), 4.02 (1H, dd, *J* = 12.4, 1.6 Hz, H-7a), 3.85 (1H, dd, *J* = 12.4, 2.1 Hz, H-7b), 3.82-3.76 (1H, m, H-10), 3.72 (1H, dq, *J* = 8.7, 1.6 Hz, H-8), 3.62 (1H, dd, *J* = 6.7, 1.5 Hz, H-9), 3.19 (1H, d,

J = 8.7 Hz, C8-O<u>H</u>), 2.48 (1H, d, *J* = 4.5 Hz, C10-O<u>H</u>), 2.33-2.26 (1H, m, H-12a), 2.21-2.13 (1H, m, H-12b), 1.77-1.68 (1H, m, H-11a), 1.61-1.51 (1H, m, H-11b), 1.44 (3H, s, C-C<u>H</u>$_3$), 1.43 (3H, s, C-C<u>H</u>$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 138.5, 115.1, 99.0, 73.9, 71.0, 65.9, 63.6, 32.0, 30.0, 29.6, 18.7; **HRMS** (ES^+) calcd. for $C_{11}H_{24}NO_4$ $[M+NH_4]^+$ 234.1700, found 234.1700.

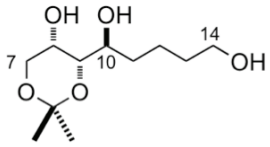
((4*S*,5*R*)-5-Hydroxy-2,2-dimethyl-1,3-dioxan-4-yl)pentane-1,5-diol (94)



To a solution of thexylBH_2 in THF (2.0 mL, 0.5 M, 1.0 mmol) at 0 ^oC was added olefin **92** (20.0 mg, 88.0 μmol) in THF (1.0 mL) dropwise. After 1 h NaOH (1.0 mL, 10% w/v) and 30% hydrogen peroxide (1.0 mL, 30% v/v) were added. The mixture was stirred for 15 min and the aqueous layer was saturated with anhydrous K_2CO_3. The organics were extracted with CH_2Cl_2 (3 × 5 mL), washed with brine (10.0 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (10% EtOAc/Hexane) to give compound **94** (17.0 mg, 85%) as a colourless oil.

***R**f* 0.11 (30% EtOAc/Hexanes); $[\alpha]_D^{20}$ -32.2 (*c* 0.5, $CHCl_3$); **IR υ_{max}** (thin film/cm^{-1}) 3367, 2931, 2870, 1454, 1376, 1277, 1067, 859; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.88 (1H, dd, *J* = 11.2, 5.4 Hz, H-7a), 3.79 (1H, td, *J* = 8.5, 5.4 Hz, H-8), 3.74 (1H, td, *J* = 7.6, 2.6 Hz, H-10), 3.68 (2H, t, *J* = 5.8 Hz, H-14), 3.61 (1H, dd, *J* = 11.2, 8.4 Hz, H-7b), 3.46 (1H, dd, *J* = 8.5, 7.1 Hz, H-9), 1.80-1.71 (1H, m, H-11a), 1.66-1.53 (4H, m, H-12, H-13), 1.52-1.45 (1H, m, H-11b), 1.45 (3H, s, C-C<u>H</u>$_3$), 1.36 (3H, s, C-C<u>H</u>$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 99.0, 75.4, 75.1, 67.2, 64.4, 62.8, 32.8, 32.2, 28.4, 21.4, 19.8; **HRMS** (ES^+) calcd. for $C_{11}H_{22}NaO_5$ $[M+Na]^+$ 257.1359, found 257.1362.

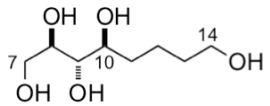
((4*S*,5*S*)-5-Hydroxy-2,2-dimethyl-1,3-dioxan-4-yl)pentane-1,5-diol (95)



To a solution of thexylBH$_2$ in THF (1.0 mL, 0.5 M, 0.5 mmol) at 0 ^{o}C was added olefin **93** (12.0 mg, 56 μmol) in THF (0.5 mL) dropwise. After 1h NaOH (0.5 mL, 10% w/v) and 30% hydrogen peroxide (0.5 mL, 30% v/v) were added. The mixture was stirred for 15 min and the aqueous layer was saturated with anhydrous K_2CO_3. The organics were extracted with CH_2Cl_2 (3 × 5 mL), washed with brine (10.0 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (10% EtOAc/Hexane) to give compound **95** (10.0 mg, 77%) as a colourless oil.

***R**f* 0.10 (30% EtOAc/Hexanes); $[\alpha]_D^{20}$ -2.4 (*c* 0.7 $CHCl_3$); **IR** υ_{max} (thin film/cm^{-1}) 3365, 2925, 2864, 1373, 1279, 1067, 976; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.02 (1H, dd, *J* = 12.4, 1.6 Hz, H-7a), 3.85 (1H, dd, *J* = 12.4, 2.0 Hz, H-7b), 3.79-3.74 (1H, m, H-10), 3.74-3.69 (1H, m, H-8), 3.66 (2H, t, *J* = 5.7 Hz, H-14), 3.61 (1H, dd, *J* = 6.7, 1.4 Hz, H-9), 3.32 (1H, d, *J* = 8.6 Hz, C8-O<u>H</u>), 2.93 (1 H, s, C10-O<u>H</u>), 1.69-1.56 (4H, m, H-12, H-13), 1.52-1.45 (2H, m, H-11), 1.44 (3H, s, C-C<u>H</u>$_3$), 1.43 (3H, s, C-C<u>H</u>$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 99.0, 74.0, 71.3, 65.9, 63.6, 62.8, 32.61, 32.41, 29.6, 21.9, 19.8; **HRMS** (ES$^+$) calcd. for $C_{11}H_{23}O_5$ $[M+H]^+$ 235.1540, found 235.1541.

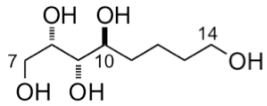
(2*R*,3*S*,4*S*)-Octane-1,2,3,4,8-pentaol (57)



To a solution of triol **94** (25.7 mg, 0.109 mmol) in MeOH (1.0 mL) and water (0.1 mL) was added Dowex-50 resin (40.0 mg) and the reaction was refluxed (65-70 ^{o}C) for 1 h. The reaction mixture was then cooled to rt, filtered and concentrated under reduced pressure to give **57** (20.8 mg, 98%) as a colourless viscous oil.

***R**f* 0.10 (10% MeOH/CH_2Cl_2); $[\alpha]_D^{20}$ -8.6 (*c* 0.3, MeOH); **IR** υ_{max} (thin film/cm^{-1}) 3239, 2860, 1406, 1205, 1149, 799; **^{1}H NMR** (500 MHz, MeOD) δ 3.77 (1H, dd, *J* = 11.1, 3.2 Hz, H-7a), 3.67 (2H, m, H-8, H-10), 3.61 (1H, dd, *J* = 11.1, 6.2 Hz, H-7b), 3.57 (2H, t, *J* = 6.4 Hz, H-14), 3.47 (1H, t, *J* = 6.4 Hz, H-9), 1.72-1.66 (1H, m, H-11a), 1.65-1.52 (3H, m, H-12a, H-13), 1.51-1.37 (2H, m, H-11b, H-12b); **^{13}C NMR** (100 MHz, MeOD) δ C9-76.0, C10-74.4, C8-73.9, C7-64.6, C14-63.0, C11-33.7, C13-33.0, C12-23.0; **HRMS** (ES^+) calcd. for $C_8H_{19}O_5$ $[M+H]^+$ 195.1227, found 195.1225.

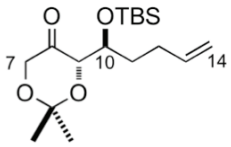
(2*S*,3*S*,4*S*)-Octane-1,2,3,4,8-pentaol (58)



To a solution of triol **95** (10.0 mg, 43 μmol) in MeOH (0.5 mL) and water (0.05 mL) was added Dowex-50 resin (30.0 mg) and the reaction was refluxed (65-70 ^oC) for 1 h. The reaction mixture was then cooled to rt, filtered and concentrated under reduced pressure to give **58** (7.5 mg, 90%) as a colourless viscous oil.

***R**f* 0.10 (10% MeOH/CH_2Cl_2); $[\alpha]_D^{20}$ -2.6 (*c* 0.8, MeOH); **IR** υ_{max} (thin film/cm^{-1}) 3358, 2930, 2869, 1454, 1376, 1207, 1157, 1066, 858; **^{1}H NMR** (400 MHz, MeOD) δ 3.90 (1H, td, *J* = 6.2, 2.0 Hz, H-8), 3.62-3.60 (3H, m, H-7, H-10), 3.57 (2H, t, *J* = 6.4 Hz, H-14), 3.34 (1H, dd, *J* = 6.5, 4.5 Hz, H-9), 1.82-1.74 (1H, m, H-11a), 1.65-1.51 (3H, m, H-12a, H-13), 1.47-1.35 (2H, m, H-11b**,** H-12b); **^{13}C NMR** (100 MHz, MeOD) δ C9-74.8, C10-72.6, C8-72.0, C7-65.0, C14-63.0, C11-34.5, C13-33.7, C12-23.0; **HRMS** (ES^+) calcd. for $C_8H_{17}O_5$ $[M-H]^-$ 193.1081, found 193.1084.

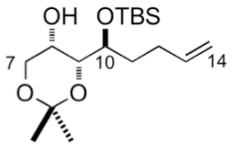
(*S*)-4-((*S*)-1-((*tert*-Butyldimethylsilyl)oxy)pent-4-en-1-yl)-2,2-dimethyl-1,3-dioxan-5-one (96)



To a solution of alcohol **86** (100 mg, 0.47 mmol) in CH_2Cl_2 (5.0 mL) at -78 ºC was added 2,6-lutidine (0.11 mL, 0.94 mmol) and TBSOTf (0.16 mL, 0.71 mmol). After 1.5 h, saturated NH_4Cl (5.0 mL) solution and CH_2Cl_2 (5.0 mL) were added. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by flash column chromatography (5% EtOAc/Hexane) provided **96** (140 mg, 95%) as a colourless oil.

R_f 0.43 (10% EtOAc/Hexanes); $[\alpha]_D^{20}$ -5.7 (*c* 1.0, $CHCl_3$); **IR υ_{max}** (thin film/cm^{-1}) 2983, 2934, 1719, 1448, 1370, 1271, 1204, 1041, 981; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.80 (1H, ddt, *J* = 16.9, 10.2, 6.7 Hz, H-13), 5.02 (1H, dt, *J* = 17.1, 1.6 Hz, H-14a), 4.98-4.94 (1H, m, H-14b), 4.25 (1H, dd, *J* = 2.6, 1.4 Hz, H-9), 4.21 (1H, dd, *J* = 16.5, 1.1 Hz, H-7a), 4.13-4.09 (1H, m, H-10), 3.93 (1H, d, *J* = 16.4 Hz, H-7b), 2.23-2.10 (1H, m, H-12a), 2.09-1.97 (1H, m, H-12b), 1.86-1.76 (1H, m, H-11a), 1.59-1.48 (1H, m, H-11b), 1.46 (3H, s, C-C$\underline{H}_3$), 1.45 (3H, s, C-C$\underline{H}_3$), 0.89 (9H, s, Si-C(C$\underline{H}_3$)$_3$), 0.10 (3H, s, Si-C$\underline{H}_3$), 0.09 (3H, s, Si-C$\underline{H}_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 208.0, 138.5, 114.8, 100.8, 78.4, 71.5, 67.4, 32.0, 30.2, 26.0, 24.5, 23.6, 18.3, -4.24, -4.43; **HRMS** (ES^+) calcd. for $C_{17}H_{33}O_4Si$ $[M+H]^+$ 329.2143, found 329.2147.

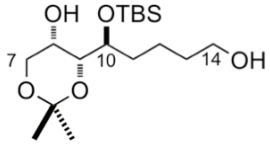
(4*R*,5*S*)-4-((*S*)-1-((*tert*-Butyldimethylsilyl)oxy)pent-4-en-1-yl)-2,2-dimethyl-1,3-dioxan-5-ol (97)



To a solution of ketone **96** (84.0 mg, 0.25 mmol) in THF (2.0 mL) at -78 ºC was added L-selectride (0.38 mL, 1M in THF, 0.38 mmol). After 1 h the reaction mixture was quenched with saturated NH_4Cl (10.0 mL) solution and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 20 mL) and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (10% EtOAc/Hexanes) to give compound **97** (78.0 mg, 93%) as a colourless oil.

R_f 0.42 (10% EtOAc/Hexanes); $[\alpha]_D^{20}$ +2.4 (*c* 1.0, $CHCl_3$); **IR υ_{max}** (thin film/cm^{-1}) 3389, 2920, 2874, 1456, 1378, 1210, 1152, 850; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.82 (1H, ddt, *J* = 17.1, 10.4, 6.7 Hz, H-13), 5.05-4.94 (2H, m, H-14), 3.99 (1H, dd, *J* = 12.4, 1.1 Hz, H-7a), 3.96-3.91 (1H, m, H-10), 3.85 (1H, dd, *J* = 12.3, 1.8 Hz, H-7b), 3.64 (2H, app d, *J* = 5.9 Hz, H-8, H-9), 3.33 (1H, d, *J* = 7.4 Hz, O<u>H</u>), 2.18-2.04 (2H, m, H-12), 1.76-1.67 (1H, m, H-11a), 1.65-1.56 (1H, m, H-11b), 1.44 (3H, s, C-C<u>H</u>$_3$), 1.43 (3H, s, C-C<u>H</u>$_3$), 0.90 (9H, s, Si-C(C<u>H</u>$_3$)$_3$), 0.14 (3H, s, Si-C<u>H</u>$_3$), 0.09 (3H, s, Si-C<u>H</u>$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 138.8, 114.6, 99.0, 72.4, 71.4, 66.3, 63.3, 32.4, 29.7, 28.4, 26.0, 18.6, 18.3, -4.46, -4.51; **HRMS** (ES^+) calcd. for $C_{17}H_{35}O_4Si$ $[M+H]^+$ 331.2299, found 331.2302.

(4*R*,5*S*)-4-((*S*)-1-((*tert*-Butyldimethylsilyl)oxy)-5-hydroxypentyl)-2,2-dimethyl-1,3-dioxan-5-ol

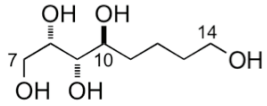


To a solution of thexylBH_2 in THF (2.0 mL, 0.5 M, 1.0 mmol) at 0 ^oC was added olefin **97** (61.0 mg, 0.18 mmol) in THF (1.0 mL) dropwise. After 2 h NaOH (1.0 mL, 10% w/v) and

30% hydrogen peroxide (1.0 mL, 30% v/v) were added. The mixture was stirred for 15 min and the aqueous layer was saturated with $NaHCO_3$ and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL), washed with brine (10 ml), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (20% EtOAc/Hexanes) to give diol (56.5 mg, 88%) as a colourless oil.

***R**f* 0.20 (10% EtOAc/Hexanes); $[\alpha]_D^{20}$ +2.2 (*c* 1.7, $CHCl_3$); **IR** υ_{max} (thin film/cm^{-1}) 3363, 2828, 2868, 1455, 1376, 1207, 1157, 1066, 859; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.98 (1H, dd, *J* = 12.3, 1.5 Hz, H-7a), 3.89-3.94 (1H, m, H-10), 3.84 (1H, dd, *J* = 12.3, 2.0 Hz, H-7b), 3.60-3.67 (4H, m, H-8, H-9, H-14), 3.42 (1H, d, *J* = 7.2 Hz, C8-O<u>H</u>), 1.52-1.61 (6H, m, H-11, H-12, H-13), 1.43 (3H, s, C-C<u>H</u>$_3$), 1.42 (3H, s, C-C<u>H</u>$_3$), 0.89 (9H, s, Si-C(C<u>H</u>$_3$)$_3$), 0.13 (3H, s, Si-C<u>H</u>$_3$), 0.08 (3H, s, Si-C<u>H</u>$_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 98.8, 72.3, 71.8, 66.2, 63.2, 62.8, 33.0, 32.8, 29.6, 25.9 (x3), 20.2, 18.5, 18.1, -4.6 (x2); **HRMS** (ES^+) calcd. for $C_{17}H_{37}O_5Si$ $[M+H]^+$ 349.2405, found 349.2405.

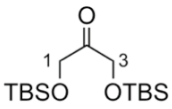
(2*S*,3*S*,4*S*)-Octane-1,2,3,4,8-pentaol (58)



To a solution of diol (16.0 mg, 0.07 mmol) in MeOH (0.5 mL) and water (0.05 mL) was added Dowex-50 resin (30.0 mg) and the reaction was refluxed (65-70 ^oC) for 1 h. The reaction mixture was then cooled to rt, filtered and concentrated under reduced pressure to give (2*R*,3*S*,4*S*)-octane-1,2,3,4,8-pentaol **58** (12.0 mg, 88%) as a colourless viscous oil.

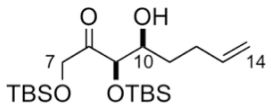
***R**f* 0.10 (10% MeOH/CH_2Cl_2); $[\alpha]_D^{20}$ -2.6 (*c* 0.8, MeOH); **IR** υ_{max} (thin film/cm^{-1}) 3358, 2930, 2869, 1454, 1376, 1207, 1157, 1066; **^{1}H NMR** (400 MHz, MeOD) δ 3.90 (1H, td, *J* = 6.2, 2.0 Hz, H-8), 3.62-3.60 (3H, m, H-7, H-10), 3.57 (2H, t, *J* = 6.4 Hz, H-14), 3.34 (1H, dd, *J* = 6.5, 4.5 Hz, H-9), 1.82-1.74 (1H, m, H-11a), 1.65-1.51 (3H, m, H-12a, H-13), 1.47-1.35 (2H, m, H-11b**,** H-12b); **^{13}C NMR** (100 MHz, MeOD) δ C9-74.8, C10-72.6, C8-72.0, C7-65.0, C14-63.0, C11-34.5, C13-33.7, C12-23.0; **HRMS** (ES^+) calcd. for $C_8H_{17}O_5$ $[M-H]^+$ 193.1081, found 193.1084.

1,3-Bis[(*tert*-butyl)dimethylsilyloxy]propan-2-one (65)[136]



To a solution of dihydroxyacetone dimer **98** (4.00 g, 22.2 mmol) in DMF (50 mL) was added TBSCl (15.9 g, 106 mmol) and imidazole (15.0 g, 222 mmol). After 24 h the reaction mixture was quenched with cold water and extracted with Et_2O (5 × 50 mL). The combined organic extracts were washed with water (100 mL), brine (100 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The resulting residue was filtered over silica gel (20% EtOAc/Hexanes) to provide ketone **65** (13.0 g, 95%) as a colourless oil.
***R**f* 0.80 (10% EtOAc/Hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.42 (4H, s, H-1, H-3), 0.92 (18H, s, Si-C($C\underline{H}_3$)$_3$), 0.09 (12H, s, Si-$C\underline{H}_3$).

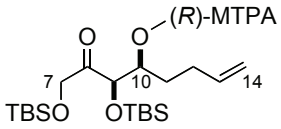
(3*R*,4*S*)-1-Hydroxypent-4-en-1-yl)-1,3-bis(*tert*-butyldimethylsilyloxy)-4-hydroxy-octane-8-one (99)



To a solution of ketone **65** (1.00 g, 3.14 mmol) in $CHCl_3$ (5.0 mL) at 0 ºC was added aldehyde **84** (132 mg, 1.57 mmol), followed by H_2O (3 vol%) and O-*t*Bu-threonine (55.0 mg, 0.31 mmol) and the reaction mixture was allowed to warm to rt. After 5 days water (5.0 mL) was added and the layers were separated. The aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by flash column chromatography (5% EtOAc/Hexanes) afforded aldol product **99** (180 mg, 28%) as a colourless oil.
***R**f* 0.10 (10% EtOAc/Hexanes); $[\alpha]_D^{20}$ +10.0 (*c* 1.0, $CHCl_3$); **IR υ_{max}** (thin film/cm^{-1}) 3491, 3079, 2954, 2931, 2887, 2858, 1735, 1472, 1255, 1100, 838, 779; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.86-5.76 (1H, m, H-13), 5.04 (1H, dq, *J* = 17.1, 1.7 Hz, H-14a), 4.98 (1H, ddt, *J* = 10.2, 1.9, 1.2 Hz, H-14b), 4.48 (2H, d, *J* = 3.2 Hz, H-7), 4.30 (1H, d, *J* = 2.9 Hz, H-9), 3.80 (1H, dddd, *J* = 10.1, 7.1, 6.2, 2.9 Hz, H-10), 2.32-2.21 (1H, m, H-12a), 2.19 (1H, d, *J*

= 10.0 Hz, O<u>H</u>), 2.17-2.08 (1H, m, H-12b), 1.60-1.55 (2H, m, H-11), 0.94 (9H, s, Si-C(C<u>H</u>$_3$)$_3$), 0.92 (9H, s, Si-C(C<u>H</u>$_3$)$_3$), 0.10 (3H, s, Si-C<u>H</u>$_3$), 0.09 (3H, s, Si-C<u>H</u>$_3$), 0.09 (3H, s, Si-C<u>H</u>$_3$), 0.07 (3H, s, Si-C<u>H</u>$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 210.3, 138.0, 115.3, 79.3, 72.5, 68.6, 33.3, 30.1, 26.0, 25.9, -4.7, -4.9, -5.3, -5.4; **HRMS** (ES^+) calcd. for $C_{20}H_{46}NO_4Si_2$ $[M + NH_4]^+$ 420.2960, found 420.2961.

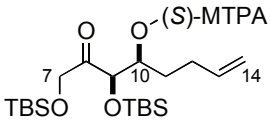
(*R*)-Mosher ester of 99 (100)



To a stirred mixture of alcohol **99** (10.0 mg, 24.8 μmol), DCC (20.0 mg, 99.2 μmol) and DMAP (6.1 mg, 50.0 μmol) in CH_2Cl_2 (1.0 mL) at rt was added (+)-(*R*)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (11.7 mg, 50.0 μmol) in one portion. After 16 h, the crude reaction mixture was purified directly by flash column chromatography (5% EtOAc/Hexanes) to give (*R*)-MTPA ester **100** (11.0 mg, 73%).

***R**$_f$* 0.26 (10% EtOAc/Hexanes); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.50-7.54 (2H, m, Ar-H, MTPA), 7.37-7.41 (3H, m, Ar-H, MTPA), 5.77 (1H, ddt, *J* = 16.8, 10.1, 6.6 Hz, H-13), 5.38 (1H, ddd, *J* = 8.3, 5.2, 2.2 Hz, H-10), 5.06-5.00 (2H, m, H-14), 4.56 (1H, d, *J* = 1.9 Hz, H-9), 4.35 (1H, d, *J* = 18.2, H-7a), 4.28 (1H, d, *J* = 18.2 Hz, H-7b), 3.47 (3H, s, MTPA-OC<u>H</u>$_3$), 2.19-2.10 (1H, m, H-12a), 2.09-2.01 (1H, m, H-12b), 1.88-1.85 (1H, m, H-11a), 1.84-1.76 (1 H, m, H-11b), 0.91 (9H, s, Si-C(C<u>H</u>$_3$)$_3$), 0.90 (9H, s, Si-C(C<u>H</u>$_3$)$_3$), 0.08 (3H, s, Si-C<u>H</u>$_3$), 0.07 (3H, s, Si-C<u>H</u>$_3$), 0.04 (3H, s, Si-C<u>H</u>$_3$), 0.03 (3H, s, Si-C<u>H</u>$_3$); **^{19}F NMR** (470 MHz; $CDCl_3$) δ -72.1, -72.6, 91% de.

(*S*)-Mosher ester of 99 (101)

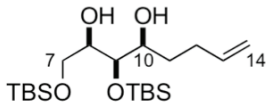


To a stirred mixture of alcohol **99** (10.0 mg, 24.8 μmol), DCC (20.0 mg, 99.2 μmol) and DMAP (6.1 mg, 50.0 μmol) in CH_2Cl_2 (1.0 mL) at rt was added (+)-(*S*)-α-methoxy-α-

(trifluoromethyl)-phenylacetic acid (11.7 mg, 50.0 μmol) in one portion. After 16 h, the crude reaction mixture was purified directly by flash column chromatography (5% EtOAc/Hexanes) to give (*S*)-MTPA ester **101** (8.0 mg, 53%).

***R**f* 0.26 (10% EtOAc/Hexanes); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.56-7.58 (2H, m, Ar-H, MTPA), 7.38-7.40 (3H, m, Ar-H, MTPA), 5.69 (1H, ddt, *J* = 16.8, 10.1, 6.6 Hz, H-13), 5.37-5.33 (1H, m, H-10), 4.99-4.89 (2H, m, H-14), 4.67 (1H, d, *J* = 1.6 Hz, H-9), 4.49 (1H, d, *J* = 18.0 Hz, H-7a), 4.28 (1H, d, *J* = 18.0 Hz, H-7b), 3.57 (3H, s, MTPA-OC$\underline{H}_3$), 1.97-1.86 (3H, m, H-11a, H-12), 1.72-1.64 (1H, m, H-11b), 0.92 (9H, s, Si-C(C$\underline{H}_3$)$_3$), 0.91 (9H, s, Si-C(C$\underline{H}_3$)$_3$), 0.10 (3H, s, Si-C$\underline{H}_3$), 0.08 (3H, s, Si-C$\underline{H}_3$), 0.07 (3H, s, Si-C$\underline{H}_3$), 0.04 (3H, s, Si-C$\underline{H}_3$).

(2*R*,3*R*,4*S*)-1,3-Bis((*tert*-butyldimethylsilyl)oxy)oct-7-ene-2,4-diol (102)



Method A

To a solution of aldol adduct **99** (25.0 mg, 62 μmol) in MeOH (2.0 mL) at -78 ºC was added $NaBH_4$ (2.9 mg, 75 μmol). After 1 h, the reaction mixture was quenched with saturated NH_4Cl (4.0 mL) solution and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (5-10% of EtOAc/Hexanes) to give inseparable mixture of compounds **102** and **103** (20.0 mg, 80%) as a colourless oil in 10:1 *syn:anti* ratio.

Method B

To a solution of aldol adduct **99** (50.0 mg, 0.12 mmol) and $CeCl_3$•$7H_2O$ (70.0 mg, 0.18 mmol) in MeOH (2.0 mL) at -78 ºC was added $NaBH_4$ (5.6 mg, 0.15 mmol). After 1 h the reaction mixture was quenched with saturated NH_4Cl (4.0 mL) solution and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (5% of EtOAc/Hexanes) to give inseparable

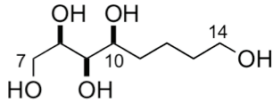
mixture of compounds **102** and **103** (30.0 mg, 61%) as a colourless oil in 10:1 *syn:anti* ratio.

Method C

To a solution of aldol adduct **99** (26.0 mg, 65.0 μmol) in THF (1.0 mL) at -78ºC was added $(c\text{-hex})_2BCl{\bullet}NEt_3$ (0.44 mL, 0.19M soln. in THF, 84.0 μmol) and after stirring for 15 min, $LiBH_3OMe$ (0.55 mL, 0.2M soln. in THF, 0.11 mmol) was added dropwise. After 3 h the reaction mixture was quenched by addition of phosphate buffer pH 7 (1.0 mL), MeOH (1.0 mL) and H_2O_2 (0.5 mL, 30% aqueous). After 30 min the resulting mixture was partitioned between H_2O (5 mL) and CH_2Cl_2 (4 × 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by flash column chromatography (5% of EtOAc/Hexanes) provided inseparable mixture of compounds **102** and **103** (22.0 mg, 84%) as a colourless oil in 10:1 *syn:anti* ratio.

102 syn: R_f 0.15 (10% EtOAc/Hexanes); $[\alpha]_D^{20}$ -6.0 (*c* 0.3, $CHCl_3$); **IR** υ_{max} (thin film/cm^{-1}) 3481, 2940, 2868, 1458, 1189, 1109, 840, 766; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.83 (1H, ddt, *J* = 17.0, 10.3, 6.6 Hz, H-13), 5.07-4.96 (2H, m, H-14), 3.71-3.65 (4H, m, H-7, H-8, H-10), 3.63-3.60 (1H, m, H-9), 2.52 (1H, br s, C8-O<u>H</u>), 2.35 (1H, d, *J* = 7.0 Hz, C10-O<u>H</u>), 2.31-2.22 (1H, m, H-12a), 2.17-2.08 (1H, m, H-12b), 1.59-1.54 (2H, m, H-11), 0.92 (9H, s, Si-(C<u>H</u>$_3$)$_3$), 0.89 (9H, s, Si-(C<u>H</u>$_3$)$_3$), 0.14 (3H, s, Si-C<u>H</u>$_3$), 0.12 (3H, s, Si-C<u>H</u>$_3$), 0.07 (6H, s, Si-(C<u>H</u>$_3$)$_2$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 138.5, 115.0, 74.7, 72.9, 70.9, 63.7, 33.6, 30.3, 26.1, 26.0, 18.4, 18.3, -4.19, -4.21, -5.19, -5.24; **HRMS** (ES^+) calcd. for $C_{20}H_{45}O_4Si_2$ $[M + H]^+$ 405.2851, found 405.2853.

(2*R*,3*R*,4*S*)-Octane-1,2,3,4,8-pentaol (55)



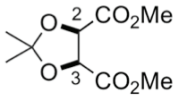
To a solution of thexylBH_2 in THF (4.0 mL, 0.5 M, 2.0 mmol) at 0 ^oC was added olefin **102** (145 mg, 0.36 mmol) in THF (2.0 mL) dropwise. After 1 h NaOH (2.0 mL, 10% w/v) and hydrogen peroxide (1 mL, 30 % v/v) were added. The mixture was stirred for 15 min and the aqueous layer was saturated with anhydrous K_2CO_3. The organics were extracted with CH_2Cl_2 (3 × 10 mL), washed with brine (20 mL), dried (Na_2SO_4), filtered and

concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (20% EtOAc/Hexanes) but due to the TBS-migration, the isolated products were directly used in the subsequent step.

To a solution of triol in MeOH (1.0 mL) and water (0.5 mL) was added Dowex-50 resin (130 mg) and the reaction was refluxed (65-70 ^{o}C) for 1 h. The reaction mixture was then cooled to rt, filtered and concentrated under reduced pressure to give **55** (55.0 mg, 80%) as a colourless viscous oil.

***R*$_f$** 0.10 (10% MeOH/CH_2Cl_2); $[\alpha]_D^{20}$ -2.0 (*c* 1.2, MeOH); **IR υ_{max}** (thin film/cm^{-1}) 3259, 2923, 2899, 1321, 1196, 1127, 1060; **^{1}H NMR** (400 MHz, MeOD) δ 3.73-3.66 (2H, m, H-8, H-10), 3.63 (2H, dd, *J* = 12.1, 5.6 Hz, H-7), 3.57 (2H, t, *J* = 6.5 Hz, H-14), 3.45 (1H, t, *J* = 4.0 Hz, H-9), 1.63-1.47 (6H, m, H-11, H-12, H-13); **^{13}C NMR** (100 MHz, MeOD) δ C9-74.3, C10-74.0, C8-73.4, C7-64.4, C14-62.9, C13-34.2, C11-33.6, C12-23.1; **HRMS** (ES$^+$) calcd. for $C_8H_{18}NaO_5$ $[M+Na]^+$ 217.1046, found 217.1047.

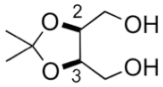
Dimethyl 2,3-*O*-Isopropylidene-*meso*-tartrate[74]



To a solution of dimethyl *meso*-tartrate **106** (1.40 g, 7.86 mmol) in DMF (10.0 mL) were added 2,2-dimethoxypropane (60.0 mL), *p*-TsOH (30.0 mg, 0.16 mmol) and the mixture was refluxed for 4h. The mixture was then cooled to rt and concentrated to a volume of ~30 mL and 1M $NaHCO_3$ (50.0 mL) was added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic extracts were washed with water (50 mL), brine (50 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by flash column chromatography (5% MeOH/CH_2Cl_2) afforded dimethylketal (1.74 g, 98%).

***R*$_f$** 0.60 (10% MeOH/CH_2Cl_2); **^{1}H NMR** (300 MHz, MeOD) δ 4.84 (2H, s, H-2, H-3), 3.75 (6H, s, OC$\underline{H}_3$), 1.65 (3H, d, *J* = 0.6 Hz, C-C$\underline{H}_3$), 1.42 (3H, d, *J* = 0.7 Hz, C-C$\underline{H}_3$).

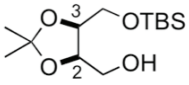
2,3-*O*-Isopropylidenethreitol (107)[74]



To a solution of dimethylketal (1.00 g, 4.59 mmol) in Et_2O (50 mL) at 0 ºC was added $LiAlH_4$ (0.384 g, 10.1 mmol). The reaction mixture was stirred at rt for 6h. Excess of $LiAlH_4$ was destroyed by addition of few drops of water and the mixture was diluted with ether and filtered. The solid residue was washed several times with MeOH and combined organic filtrates were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (5% MeOH/CH_2Cl_2) to give diol **107** (599 mg, 81%).

***R*$_f$** 0.30 (10% MeOH/CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.31-4.26 (2H, m, H-2, H-3), 3.84-3.72 (4H, m, H-1, H-4), 1.46 (3H, s, C-C$\underline{H}_3$), 1.38 (3H, s, C-C$\underline{H}_3$).

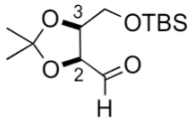
4-*O*-(*tert*-Butyldimethyl)silyl-2,3-O-isopropylidene-DL-erythritol[74]



To a solution of diol **107** (599 mg, 3.69 mmol) in THF (10.0 mL) at 0 ºC was added NaH (212 mg, 60% dispersion in mineral oil, 8.86 mmol). The mixture was allowed to stir for 15 min and TBSCl (556 mg, 3.69 mmol) was added. After 6 h, water (10.0 mL) was added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts were washed with brine (40 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by flash column chromatography (10% EtOAc/Hexanes) provided alcohol (897 mg, 88%) as a colourless oil.

***R*$_f$** 0.25 (20% EtOAc/Hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.35 (1H, dt, *J* = 7.3, 5.7 Hz, H-3), 4.23 (1H, ddd, *J* = 9.1, 6.0, 4.1 Hz, H-2), 3.84-3.73 (3H, m, H-1a, H-4), 3.68 (1H, dd, *J* = 10.5, 4.1 Hz, H-1b), 3.01 (1H, dd, *J* = 8.4, 5.6 Hz, O$\underline{H}$), 1.41 (3H, s, C-C$\underline{H}_3$), 1.35 (3H, s, C-C$\underline{H}_3$), 0.90 (9 H, s, Si-C(C$\underline{H}_3$)$_3$), 0.11 (3H, s, Si-C$\underline{H}_3$), 0.10 (3H, s, Si-C$\underline{H}_3$).

4-*O*-*tert*-Butyldimethylsilyl-2,3-*O*-isopropylidene-DL-erythrose (105)[74]

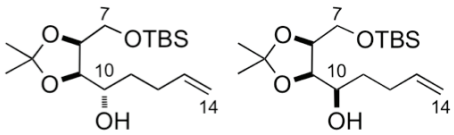


To a solution of oxalyl chloride (286 µL, 3.38 mmol) in CH_2Cl_2 (20.0 mL) at -78 ºC was added a solution of DMSO (479 µL, 6.75 mmol) in CH_2Cl_2 (5.0 mL) dropwise. The reaction mixture was stirred at -78 ºC for 15 min and a solution of alcohol (850 mg, 3.07 mmol) in CH_2Cl_2 (10.0 mL) was added. The reaction mixture was stirred at -78 ºC for an additional 15 min. and Et_3N (2.14 mL, 15.3 mmol) was then added, and the mixture was allowed to warm to rt. The reaction was quenched by addition of water (20.0 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with saturated NH_4Cl (50 mL) solution and brine (50 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The resulting oil was purified by flash column chromatography (10% EtOAc/Hexanes) to give **105** (810 mg, 96%) as a colourless oil.

R_f 0.44 (20% EtOAc/Hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.68 (1H, d, *J* = 2.0 Hz, H-1), 4.46 (1H, dd, *J* = 3.8, 2.8 Hz, H-3), 4.42 (1H, dd, *J* = 7.9, 2.0 Hz, H-2), 3.78 (1H, dd, *J* = 11.4, 3.8 Hz, H-4a), 3.69 (1H, dd, *J* = 11.4, 2.7 Hz, H-4b), 1.56 (3H, s, C-C$\underline{H}_3$), 1.38 (3H, s, C-C$\underline{H}_3$), 0.87 (9H, s, Si-C(C$\underline{H}_3$)$_3$), 0.05 (3H, s, Si-C$\underline{H}_3$), 0.04 (3H, s, Si-C$\underline{H}_3$).

(*S*)-1-((4*R*,5*S*)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-4-en-1-ol (108)

(*R*)-1-((4*R*,5*S*)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-4-en-1-ol (109)



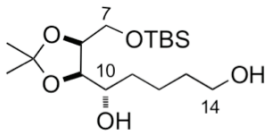
To a flame dried round bottom flask charged with magnesium turnings (1.09 g, 45.2 mmol) was added Et_2O (5.0 mL) and catalytic amount of iodine. Homoallyl bromide (5.08 g, 37.7 mmol) dissolved in THF (12.0 mL) was added dropwise as the temperature was increased to 50 ºC. The reaction mixture was stirred for 2 h.

To a solution of aldehyde **105** (0.25 g, 0.91 mmol) in THF (5.0 mL) at -40 ºC was added freshly prepared homoallyl magnesium bromide (1.24 mL, 2M soln. in THF, 2.73 mmol) *via* cannula. The resulting black solution was allowed to warm to -20 ºC for 1 h, and finally to 0 ºC for 2 h, before being quenched by the addition of saturated NH_4Cl (10.0 mL) solution and diluted with Et_2O (20 mL). The organic phase was separated, and the aqueous layer extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by flash column chromatography (5% EtOAc/Hexanes) gave hydroxy olefins **108** (230 mg, 70%) and **109** (80.0 mg, 28 %) as colourless oils.

108: R_f 0.25 (20% EtOAc/Hexanes); **IR** υ_{max} (thin film/cm^{-1}) 3484, 2953, 2931, 2860, 1472, 1368, 1177, 1082, 837, 779; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.81-5.91 (1H, m, H-13), 5.05 (1H, dq, *J* = 17.1, 1.8 Hz, H-14a), 4.96 (1H, ddt, *J* = 10.2, 2.2, 1.1 Hz, H-14b), 4.23 (1H, ddd, *J* = 10.2, 5.4, 3.4 Hz, H-8), 4.02 (1H, dd, *J* = 9.3, 5.4 Hz, H-7a), 3.93 (1H, dd, *J* = 3.1, 1.6 Hz, H-9), 3.82-3.76 (2H, m, H-10, O<u>H</u>), 3.57 (1H, dd, *J* = 10.4, 3.1 Hz, H-7b), 2.40-2.30 (1H, m, H-12a), 2.23-2.13 (1H, m, H-12b), 1.89-1.80 (1H, m, H-11a), 1.62-1.56 (1H, m, H-11b), 1.36 (3H, s, C-C<u>H</u>$_3$), 1.33 (3H, s, C-C<u>H</u>$_3$), 0.91 (9H, s, Si-C(C<u>H</u>$_3$)$_3$), 0.12 (3H, s, Si-C<u>H</u>$_3$), 0.12 (3H, s, Si-C<u>H</u>$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 138.9, 114.7, 108.5, 80.9, 68.4, 62.1, 33.3, 29.6, 28.2, 25.9, 25.5, 18.3, -5.45, -5.54; **HRMS** (ES^+) calcd. for $C_{17}H_{35}O_4Si$ $[M+H]^+$ 331.2299, found 331.2303.

109: R_f 0.24 (20% EtOAc/Hexanes); **IR** υ_{max} (thin film/cm^{-1}) 3484, 2953, 2931, 2860, 1472, 1368, 1177, 1082, 837, 779; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.83 (1H, ddt, *J* = 17.0, 10.3, 6.7 Hz, H-13), 5.04 (1H, dq, *J* = 17.1, 1.8 Hz, H-14a), 4.96 (1H, ddt, *J* = 10.1, 2.1, 1.1 Hz, H-14b), 4.15 (1H, ddd, *J* = 7.2, 6.4, 4.2 Hz, H-8), 4.02 (1H, dd, *J* = 6.4, 3.6 Hz, H-9), 3.91 (1H, dd, *J* = 10.8, 7.3 Hz, H-7a), 3.81 (1H, td, *J* = 8.8, 4.2 Hz, H-10), 3.72 (1H, dd, *J* = 10.8, 4.2 Hz, H-7b), 2.81 (1H, d, *J* = 5.1 Hz, O<u>H</u>), 2.30-2.26 (1H, m, H-12a), 2.18-2.14 (1H, m, H-12b), 1.70-1.61 (2H, m, H-11), 1.47 (3H, s, C-C<u>H</u>$_3$), 1.36 (3H, s, C-C<u>H</u>$_3$), 0.90 (9H, s, Si-C(C<u>H</u>$_3$)$_3$), 0.09 (6H, s, Si-(C<u>H</u>$_3$)$_2$); **^{13}C NMR** δ (100 MHz, $CDCl_3$) 138.5, 114.9, 108.2, 79.8, 68.4, 61.9, 33.8, 30.2, 27.5, 26.0, 25.2, 18.4, -5.3; **HRMS** (ES^+) calcd. for $C_{17}H_{35}O_4Si$ $[M+H]^+$ 331.2299, found 331.2305.

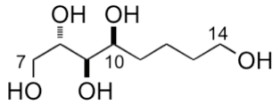
7-*O-tert*-Butyldimethylsilyl-8,9-O-isopropylidene-10-(*R*)-hydroxyocta-14-ol



To a solution of thexylBH$_2$ in THF (4.0 mL, 0.5 M, 2.0 mmol) at 0 ^{o}C was added olefin **108** (110 mg, 0.33 mmol) in THF (1.0 mL) dropwise. After 1h NaOH (0.5 mL, 10% w/v) and hydrogen peroxide (0.5 mL, 30 % v/v) were added. The mixture was stirred for 15 min and the aqueous layer was saturated with anhydrous K_2CO_3. The organics were extracted with CH_2Cl_2 (3 × 5 mL), washed with brine (15.0 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc/Hexanes) to give diol (114 mg, 95%) as a colourless oil.

***R**f* 0.16 (20% EtOAc/Hexanes); **IR** υ_{max} (thin film/cm^{-1}) 3448, 3409, 2950, 2930, 2858, 1472, 1380, 1275, 1083, 837, 777; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.17-4.11 (1H, m, H-8), 4.02 (1H, dd, *J* = 6.3, 3.5 Hz, H-9), 3.91 (1H, dd, *J* = 10.8, 7.1 Hz, H-7a), 3.81-3.77 (1H, m, H-10), 3.73 (1H, dd, *J* = 10.8, 4.1 Hz, H-7b), 3.66 (2H, t, *J* = 6.3 Hz, H-14), 1.66-1.56 (6H, m, H-11, H-12, H-13), 1.47 (3H, s, C-C$\underline{H}_3$), 1.36 (3H, s, C-C$\underline{H}_3$), 0.90 (9H, s, Si-C(C$\underline{H}_3$)$_3$), 0.09 (6H, s, Si-(C$\underline{H}_3$)$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 108.2, 79.8, 69.0, 63.0, 61.8, 34.3, 32.8, 31.1, 27.5, 26.0, 25.2, 22.3, 18.4, -5.3; **HRMS** (ES^{+}) calcd. for $C_{17}H_{37}O_5Si$ $[M+H]^{+}$ 349.2405, found 349.2407.

(2*S*,3*R*,4*S*)-Octane-1,2,3,4,8-pentaol (56)



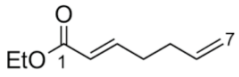
To a solution of diol (90.0 mg, 0.26 mmol) in MeOH (1.0 mL) and water (0.5 mL) was added Dowex-50 resin (90.0 mg) and the reaction was refluxed (65-70 ^{o}C) for 1 h. The reaction mixture was then cooled to rt, filtered and concentrated under reduced pressure to give **56** (49.0 mg, 98%) as a colourless viscous oil.

***R**f* 0.10 (10% MeOH/CH_2Cl_2); **IR** υ_{max} (thin film/cm^{-1}) 3342, 3244, 2926, 2911, 2860, 1405, 1281, 1087, 1026; **^{1}H NMR** (400 MHz, MeOD) δ 3.82 (1H, td, *J* = 4.3, 1.7 Hz, H-

10), 3.79 (1H, dd, *J* = 11.1, 3.5 Hz, H-7a), 3.68 (1H, ddd, *J* = 8.0, 5.9, 3.5 Hz, H-8), 3.61 (1H, dd, *J* = 11.1, 6.0 Hz, H-7b), 3.57 (2H, t, *J* = 6.5 Hz, H-14), 3.36 (1H, dd, *J* = 10.9, 5.9 Hz, H-9), 1.63-1.49 (5H, m, H-11, 12a, 13), 1.45-1.37 (1H, m, H-12b); **^{13}C NMR** (100 MHz, MeOD) δ C9-74.5, C10-73.2, C8-71.4, C7-65.1, C14-62.9, C11-34.5, C13-33.7, C12-23.4; **HRMS** (ES^+) calcd. for $C_8H_{19}O_5$ $[M+H]^+$ 195.1227, found 195.1227.

7.4 Experimental procedures for Chapter 3

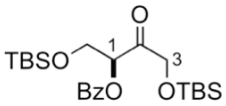
(*E*)-Ethyl-hepta-2,6-dienoate (111)[137]



To a solution of triethyl phosphonoacetate **112** (3.54 mL, 17.8 mmol), lithium chloride (2.01 g, 47.6 mmol) and Hünig's base (1.88 mL, 10.8 mmol) in MeCN (40.0 mL) at rt was added a solution of aldehyde **84** (1.00 g, 11.9 mmol) in MeCN (5.0 mL). After 18 h, the reaction was quenched by addition of H_2O (50.0 mL) and layers were separated. The aqueous phase was extracted with Et_2O (3 × 40 mL) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by flash column chromatography (5% Et_2O/Pet. Ether) provided **19** (1.51 g, 81%) as a colourless oil.

***R*$_f$** 0.42 (20% Et_2O/Pet. Ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.95 (1H, dt, *J* = 15.7, 6.7 Hz, H-3), 5.82 (1H, dt, *J* = 15.6, 1.6 Hz, H-2), 5.83-5.74 (1H, m, H-6), 5.04 (1H, dq, *J* = 17.1, 1.7 Hz, H-7a), 5.00 (1H, ddt, *J* = 10.2, 1.8, 1.2 Hz, H-7b), 4.17 (2H, q, *J* = 7.1 Hz, O$\underline{H}_2$CH$_3$), 2.33-2.27 (2H, m, H-4), 2.24-2.18 (2H, m, H-5), 1.27 (3H, t, *J* = 7.1 Hz, OCH$_2$C$\underline{H}_3$).

(1*S*)-3-(*tert*-Butyldimethylsilyloxy)-1-(*tert*-butyldimethylsilyloxymethyl)-2-oxopropyl benzoate 119[78]



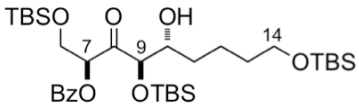
To a solution of pre-dried L-erythrulose **118** (6.00 g, 50.0 mmol) in DMF (60.0 mL) was added TBSCl (16.6 g, 110 mmol) and imidazole (10.2 g, 150 mmol). The reaction mixture was then stirred at rt for 2 h and a saturated NH_4Cl (100 mL) solution was added. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with H_2O (50 mL), brine (100 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by flash column chromatography (2-10% EtOAc/Hexanes) provided bis-TBS-ether (12.2 g, 70%) as a colourless oil, which was directly used in the next step.

***R*$_f$** 0.36 (10% EtOAc/Hexanes); **^{1}H NMR** (400 MHz; $CDCl_3$) δ 4.45 (2H, d, *J* = 17.9 Hz, H-3a), 4.44 (1H, dt, *J* = 6.7, 3.4 Hz, H-1), 4.38 (1H, d, *J* = 17.8 Hz, H-3b), 4.09 (1H, dd, *J* = 10.6, 3.3 Hz, C$\underline{H}_2$-OTBS), 3.82 (1H, dd, *J* = 10.6, 3.7 Hz, C$\underline{H}_2$-OTBS), 3.44 (1H, d, *J* = 6.7 Hz, O$\underline{H}$), 0.91 (9H, s, Si-C(C$\underline{H}_3$)$_3$), 0.85 (9H, s, Si-C(C$\underline{H}_3$)$_3$), 0.09 (3H, s, Si-C$\underline{H}_3$), 0.08 (3H, s, Si-C$\underline{H}_3$), 0.04 (6H, s, Si-(C$\underline{H}_3$)$_2$).

To a solution of bis-TBS-ether (12.1 g, 34.7 mmol) in CH_2Cl_2 (200 mL) was added Et_3N (6.25 mL, 44.7 mmol), DMAP (1.26 g, 10.3 mmol) and benzoyl chloride (4.40 mL, 38.0 mmol) dropwise. The reaction mixture was then stirred at rt for 5 h and quenched with water (200 mL) and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 200 mL), and the combined organic extracts were washed with saturated NH_4Cl (50 mL) solution, brine (100 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by flash column chromatography (2% EtOAc/Hexanes) provided ketone **119** (9.34 g, 60%) as a colourless oil.

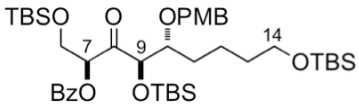
***R*$_f$** 0.68 (10% EtOAc/Hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.08 (2H, m, Ar-H), 7.58 (1H, m, Ar-H), 7.46 (2H, m, Ar-H), 5.57 (1H, dd, *J* = 4.6, 3.6 Hz, H-1), 4.49 (2H, s, H-3), 4.20 (1H, dd, *J* = 11.1, 4.6 Hz, CH_2-OTBS), 4.07 (1H, dd, *J* = 11.1, 3.6 Hz, CH_2-OTBS), 0.93 (9H, s, Si-C(CH_3)$_3$), 0.88 (9H, s, Si-C(CH_3)$_3$), 0.11 (3H, s, Si-CH_3), 0.11 (3H, s, Si-CH_3), 0.08 (3H, s, Si-CH_3), 0.07 (3H, s, Si-CH_3).

(1*R*,3*R*,4*R*)-3,8-Bis(*tert*-butyldimethylsilyloxy)-1-(*tert*-butyldimethylsilyloxymethyl)-4-hydroxy-2-oxooctyl benzoate (123)



To a stirred solution of ketone **119** (1.18 g, 2.62 mmol) in Et_2O (20.0 mL) at -78 ºC was added dicyclohexylboron chloride (1.03 mL, 4.71 mmol) and Et_3N (0.728 mL, 5.24 mmol) and the reaction mixture was stirred for 0.5 h. Aldehyde **69** (0.85 g, 3.9 mmol) in Et_2O (10.0 mL) was then added and stirring was continued for 2 h. The reaction mixture was then diluted with MeOH (5.0 mL) and phosphate buffer pH 7 (5.0 mL) was added followed by H_2O_2 (5.0 mL, 30% v/v). The biphasic mixture was allowed to warm to rt and stirred vigorously for 10 min. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 30 mL), washed with brine (30 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Flash column chromatography (5% EtOAc/Hexanes) provided aldol adduct **123** (1.40 g, 81%) as a 4:1 inseparable mixture of diastereoisomers.
R_f 0.34 (10% EtOAc/Hexanes); **IR υ_{max}** (thin film/cm^{-1}) 3491, 2938, 2892, 2861, 1724, 1463, 1267, 1105, 839, 778; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.10-8.06 (2H, m, Ar-H), 7.61-7.56 (1H, m, Ar-H), 7.48-7.43 (2H, m, Ar-H), 5.72 (1H, dd, *J* = 4.9, 3.5 Hz, H-7), 4.20 (1H, d, *J* = 5.4 Hz, H-9), 4.15 (2H, dd, *J* = 4.2, 1.9 Hz, H-6), 3.92-3.86 (1H, m, H-10), 3.60 (2H, t, *J* = 6.3 Hz, H-14), 3.08 (1H, d, *J* = 7.5 Hz, OH), 1.64-1.49 (5H, m, H-11, H-12a, H-13), 1.49-1.37 (1H, m, H-12b), 0.93 (9H, s, Si-C$(CH_3)_3$), 0.88 (9H, s, Si-C$(CH_3)_3$), 0.87 (9H, s, Si-C$(CH_3)_3$), 0.12 (6H, s, Si-$(CH_3)_2$), 0.10 (3H, s, Si-CH_3), 0.09 (3H, s, Si-CH_3), 0.07 (3H, s, Si-CH_3), 0.04 (3H, s, Si-CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 205.1, 166.5, 133.6, 130.1, 129.4, 128.6, 81.9, 79.1, 73.9, 63.2, 62.8, 32.8, 32.6, 26.1, 26.0, 25.9, 22.3, 18.5, 18.4, 18.3, -4.4, -4.6, -5.1, -5.2; **HRMS** (ES^+) calcd. for $C_{34}H_{65}O_7Si_3$ $[M+H]^+$ 669.4033, found 669.4020.

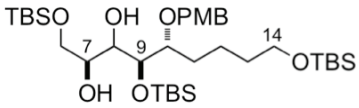
(1*R*,3*R*,4*R*)-3,8-Bis(*tert*-butyldimethylsilyloxy)-1-(*tert*-butyldimethylsilyloxymethyl)-4-(methoxybenzyl)oxy-2-oxooctyl benzoate (125)



To a solution of alcohol **123** (1.40 g, 2.09 mmol) and PMBTCA (886 mg, 3.14 mmol) in PhMe (20.0 mL) at 0 ºC was added lanthanum (III) triflate (61.0 mg, 0.104 mmol). After 6 h, cold hexane (40.0 mL) was added and the precipitate was filtered. The resulting mixture was concentrated under reduced pressure and purified by flash column chromatography (5% EtOAc/Hexanes) to give PMB ether **125** (1.08 g, 65%) as a colourless oil.

R_f 0.44 (10% EtOAc/Hexanes); $[\alpha]_D^{20}$ +7.6 (*c* 2.5, $CHCl_3$); **IR υ_{max}** (thin film/cm^{-1}) 2933, 2891, 2859, 1725, 1610, 1466, 1255, 1104, 837, 778, 711; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.08 (2H, dd, *J* = 8.4, 1.3 Hz, Ar-H), 7.56 (1H, s, Ar-H), 7.45 (2H, t, *J* = 7.7 Hz, Ar-H), 7.19 (2H, d, *J* = 8.7 Hz, PMB Ar-H), 6.83 (2H, d, *J* = 8.7 Hz, PMB Ar-H), 5.87 (1H, t, *J* = 4.5 Hz, H-7), 4.63 (1H, d, *J* = 3.4 Hz, H-9), 4.50 (1H, d, *J* = 11.2 Hz, CH_aH_bAr), 4.36 (1H, d, *J* = 11.2 Hz, CH_aH_bAr), 4.08 (2H, d, *J* = 4.5 Hz, H-6), 3.79 (3H, s, Ar-OCH_3), 3.71 (1H, dt, *J* = 8.4, 3.3 Hz, H-10), 3.54 (2H, td, *J* = 6.3, 1.5 Hz, H-14), 1.73-1.63 (1H, m, H-11a), 1.51-1.38 (4H, m, H-11b, H-12a, H-13), 1.33-1.21 (1H, m, H-12b), 0.94 (9H, s, Si-$C(CH_3)_3$), 0.88 (9H, s, Si-$C(CH_3)_3$), 0.84 (9H, s, Si-$C(CH_3)_3$), 0.12 (3H, s, 2 × Si-CH_3), 0.09 (3H, s, 2 × Si-CH_3), 0.05 (3H, s, Si-CH_3), 0.02 (6H, s, 2 × Si-CH_3), 0.02 (3H, s, Si-CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 205.7, 165.6, 159.2, 133.3, 130.4, 130.0, 129.9, 129.5, 128.5, 113.8, 81.4, 78.3, 78.0, 71.9, 63.3, 62.1, 55.3, 33.0, 29.8, 26.14, 26.12, 25.9, 21.9, 18.51, 18.48, 18.37, -4.0, -4.8, -5.1, -5.3; **HRMS** (ES^+) calcd. for $C_{42}H_{76}NO_8Si_3$ $[M+NH_4]^+$ 806.4873, found 806.4875.

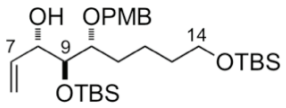
(1*R*,3*S*,4*R*)-3,8-Bis(*tert*-butyldimethylsilyloxy)-1-(*tert*-butyldimethylsilyloxymethyl)-4-(methoxybenzyl)oxy-octane-1,2-diol (126)



To a solution of keto-ester **125** (729 mg, 0.92 mmol) in Et_2O (20.0 mL) at –78 ºC was added $LiBH_4$ (1.85 mL, 2M soln. in THF, 3.69 mmol) dropwise. The reaction mixture was stirred for 2 h and quenched with saturated $NaHCO_3$ (50.0 mL) solution. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (10% EtOAc/Hexanes) provided diol **126** (415 mg, 66%) as a colourless oil.

R_f 0.24 (10% EtOAc/Hexanes); $[\alpha]_D^{20}$ +10.1 (*c* 0.8 $CDCl_3$); **IR υ_{max}** (thin film/cm^{-1}) 3316, 3259, 2923, 2899, 1321, 1196, 1127, 1060; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.26 (2H, d, *J* = 8.6 Hz, Ar-H), 6.86 (2H, d, *J* = 8.7 Hz, Ar-H), 4.65 (1H, d, *J* = 10.8 Hz, CH_aH_bAr), 4.44 (1H, d, *J* = 10.9 Hz, CH_aH_bAr), 3.96 (1H, dd, *J* = 4.8, 3.2, H-10), 3.80 (3H, s, Ar-OCH_3), 3.71-3.52 (7H, m, H-6, H-7, H-8, H-9, H-14), 3.19 (1H, d, *J* = 5.0 Hz, C8-OH), 2.95 (1H, d, *J* = 4.5 Hz, C7-OH), 1.59-1.47 (5H, m, H-11, H-12a, H-13), 1.28-1.26 (1H, m, H-12b), 0.92 (9H, s, Si-$C(CH_3)_3$), 0.90 (18H, s, Si-$C(CH_3)_3$), 0.12 (3H, s, Si-CH_3), 0.11 (3H, s, Si-CH_3), 0.07 (6H, s, 2 × Si-CH_3), 0.04 (6H, s, 2 × Si-CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.3, 130.5, 129.6, 113.9, 82.3, 73.8, 72.7, 71.1, 70.9, 64.8, 63.3, 55.4, 33.1, 30.7, 26.15, 26.13, 26.10, 22.5, 18.53, 18.49, 18.33, -3.9, -4.6, -5.10, -5.21; **HRMS** (ES^+) calcd. for $C_{35}H_{72}O_7Si_3$ $[M+H]^+$ 687.4502, found 687.4495.

(3*S*,4*S*,5*R*)-4,9-Bis((*tert*-butyldimethylsilyl)oxy)-5-((4-methoxybenzyl)oxy)nonen-3-ol (128)



To a solution of diol **126** (0.39 g, 0.58 mmol) in EtOAc (20.0 mL) was added $Pb(OAc)_4$ (0.41 mg, 0.58 mmol), resulting in a light yellow suspension. After 10 min of stirring, the mixture was filtered through a plug of silica gel, eluting with EtOAc to afford aldehyde **127** (0.28 g, 97%) as a colourless oil immediately used without further purification.

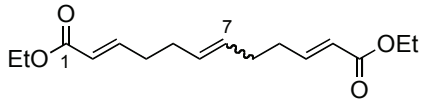
***R**f* 0.36 (10% EtOAc/Hexanes); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.67 (1H, d, *J* = 1.6 Hz, H-8), 7.24 (2H, d, *J* = 8.7 Hz, Ar-H), 6.86 (2H, d, *J* = 8.7 Hz, Ar-H), 4.60 (1H, d, *J* = 11.1 Hz, CH_aH_bAr), 4.47 (1H, d, *J* = 11.2 Hz, CH_aH_bAr), 4.09 (1H, dd, *J* = 3.6, 1.7 Hz, H-9), 3.80 (3H, s, Ar-OCH_3), 3.62 (1H, dt, *J* = 5.7, 2.9 Hz, H-10), 3.58 (1H, t, *J* = 6.1 Hz, H-14), 1.72-1.63 (1H, m, H-11a), 1.56-1.42 (5H, m, H-11b, H-12, H-13), 0.93 (9H, s, Si-$C(CH_3)_3$), 0.89 (9H, s, Si-$C(CH_3)_3$), 0.08 (6H, s, 2 × Si-CH_3), 0.04 (6H, s, 2 × Si-CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 203.8, 159.4, 130.4, 129.6, 113.9, 81.1, 79.6, 72.3, 63.2, 55.4, 32.9, 30.8, 26.1, 25.9, 22.0, 18.52, 18.36, -4.58, -4.71, -5.1.

To a solution of aldehyde **127** (370 mg, 0.72 mmol) in THF (20.0 mL) at -78 ºC was added vinylmagnesium bromide (6.2 mL, 0.7M soln. in THF, 4.35 mmol). The reaction mixture was allowed to warm up to 0 ºC over 12h. The reaction was quenched with saturated NH_4Cl (20.0 mL) solution and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 50 mL) and the combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Flash column chromatography (5% EtOAc/Hexanes) provided allylic alcohol **128** (199 mg, 52%) as a colourless oil.

***R**f* 0.34 (20% EtOAc/Hexanes); $[\alpha]_D^{20}$ +15.3 (*c* 1.6, $CHCl_3$); **IR υ_{max}** (thin film/cm^{-1}) 3364, 2933, 2891, 2860, 1464, 1317, 1099, 837, 774; **^{1}H NMR** (400 MHz; $CDCl_3$) δ 7.25 (2H, d, *J* = 8.7 Hz, Ar-H), 6.86 (2H, d, *J* = 8.7 Hz, Ar-H), 5.97 (1H, ddd, *J* = 17.3, 10.5, 6.1 Hz, H-2), 5.30 (1H, dt, *J* = 17.3, 1.6 Hz, H-6a), 5.18 (1H, dt, *J* = 10.5, 1.5 Hz, H-6b), 4.53 (1H, d, *J* = 11.0 Hz, CH_aH_bAr), 4.41 (1H, d, *J* = 10.9 Hz, CH_aH_bAr), 4.26-4.22 (1H, m, H-8), 3.80 (3H, s, Ar-OCH_3), 3.75 (1H, dd, *J* = 4.9, 4.1 Hz, H-9), 3.59 (2H, t, *J* = 6.3 Hz, H-14), 3.50-3.46 (1H, m, H-10), 2.26 (1H, d, *J* = 4.0 Hz, OH), 1.66-1.57 (2H, m, H-11), 1.54-1.45 (3H,

m, H-12a, H-13), 1.40-1.30 (1H, m, H-12b), 0.90 (9H, s, Si-C(C<u>H</u>$_3$)$_3$), 0.89 (9H, s, Si-C(C<u>H</u>$_3$)$_3$), 0.08 (6H, s, 2 × Si-C<u>H</u>$_3$), 0.04 (6H, s, 2 × Si-C<u>H</u>$_3$); **^{13}C NMR** (100 MHz; $CDCl_3$) δ 159.3, 137.9, 130.9, 129.5, 116.2, 113.8, 80.9, 76.8, 75.0, 72.1, 63.4, 55.4, 33.2, 30.8, 26.15, 26.13, 22.1, 18.5, 18.4, -4.1, -4.2, -5.1; **HRMS** (ES^+) calcd. for $C_{29}H_{55}O_5Si_2$ $[M+H]^+$ 539.3583, found 539.3598.

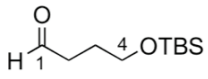
Diethyl 2,6,10-dodecatrienedioate (135)[138]



To a stirred solution of Grubbs II cat. (7.60 mg, 9.27 μmol) in CH_2Cl_2 (5.0 mL) at rt was added a solution of olefin **111** (57.0 mg, 0.371 mmol) and **128** (50.0 mg, 92.8 μmol) in CH_2Cl_2 (5.0 mL) and the mixture was stirred for 24 h. Following concentration, the crude product was purified by flash column chromatography (10% EtOAc:Pet.Ether) to provide dimer of the olefin **176** as a colourless oil (30.0 mg, 30%) and returned unreacted olefin **128** (20.0 mg).

R$_f$ 0.38 (20% EtOAc/Hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.94 (2H, dt, *J* = 15.7, 6.8 Hz, H-3, 3'), 5.81 (2H, dt, *J* = 15.7, 1.6 Hz, H-2, 2'), 5.44 (2H, tt, *J* = 3.4, 1.7 Hz, H-6, H-7), 4.18 (4H, q, *J* = 7.1 Hz, OC<u>H</u>$_2$CH$_3$), 2.28-2.23 (4H, m, H-4, 4'), 2.18-2.14 (4H, m, H-5, 5'), 1.28 (6H, t, *J* = 7.1 Hz, OCH$_2$C<u>H</u>$_3$); **^{13}C NMR** (100 MHz; $CDCl_3$) δ 166.8, 148.5, 129.9, 121.8, 60.3, 32.2, 31.0, 14.4.

4-(*tert*-Butyldimethylsilyl)oxy-butanal (145)[139,140]



To a solution of 1,4-butanediol **146** (9.80 mL, 0.11 mol), Et_3N (6.75 mL, 48 mmol) and DMAP (450 mg, 3.7 mmol) in CH_2Cl_2 (40.0 mL) at rt was slowly added a solution of TBSCl (5.60 g, 37.1 mmol) in CH_2Cl_2 (10.0 mL). After 16 h, the reaction mixture was poured onto brine (50.0 mL) and layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic extracts were washed with water (100

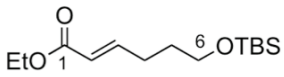
mL), brine (50 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by flash column chromatography (5% EtOAc/Hexanes) provided alcohol (6.42 g, 86%) as a colourless oil.

***R*$_f$** 0.43 (50% EtOAc/Hexanes); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.67 (4H, m, H-1, H-4), 2.51 (1H, t, *J* = 5.8 Hz, O<u>H</u>), 1.66 (4H, m, H-2, H-3), 0.91 (9H, s, Si-C(C<u>H</u>$_3$)$_3$), 0.08 (6H, m, Si-(C<u>H</u>$_3$)$_2$).

To a solution of oxalyl chloride (3.39 mL, 39.2 mmol) in CH_2Cl_2 (50.0 mL) at -78 ºC was slowly added DMSO (3.33 mL, 47.1 mmol). After 30 min, a solution of alcohol (4.00 g, 19.6 mmol) in CH_2Cl_2 (20.0 mL) was added, dropwise. After 1 h, Et_3N (19.1 mL, 137 mmol) was added and the slurry was allowed to attain rt. After 1 h, saturated NH_4Cl (50 mL) solution was added and layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 40 mL) and the combined organic extracts were washed with H_2O (100 mL), brine (100 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude aldehyde **145** (3.17 g, 80%) was used without further purification.

***R*$_f$** 0.71 (25% EtOAc/Hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.80 (1H, t, *J* = 1.7 Hz, H-1), 3.66 (2H, t, *J* = 5.9 Hz, H-4), 2.51 (2H, dt, *J* = 7.2, 1.7 Hz, H-2), 1.87 (2H, m, H-3), 0.89 (9H, s, Si-C(C<u>H</u>$_3$)$_3$), 0.05 (6H, m, 2 × Si-C<u>H</u>$_3$).

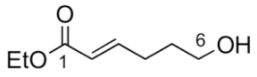
(*E*)-Methyl-6-(*tert*-Butyldimethylsilyl)oxy-hex-2-enoate (147)[141]



To a solution of triethyl phosphonoacetate **112** (4.04 mL, 20.3 mmol), lithium chloride (3.71 g, 87.6 mmol) and Hünig's base (2.28 mL, 13.1 mmol) in MeCN (50.0 mL) at rt was added a solution of aldehyde **145** (3.15 g, 15.6 mmol) in MeCN (20.0 mL). After 18 h, H_2O (50.0 mL) was added and the layers were separated. The aqueous phase was extracted with EtOAc (3 × 40 mL) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by flash column chromatography (5% EtOAc/Hexanes) provided **147** (3.29 g, 77%) as a colourless oil.

***R*$_f$** 0.52 (20% EtOAc/Hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.95 (1H, dt, *J* = 15.6, 6.9 Hz, H-3), 5.85 (1H, dt, *J* = 15.6, 1.6 Hz, H-2), 4.15 (2H, q, *J* = 7.1 Hz, OC<u>H</u>$_2$CH$_3$), 3.60 (2H, t, *J* = 7.1 Hz, H-6), 2.3 (2H, m, H-4), 1.65 (2H, m, H-5), 1.25 (3H, t, *J* = 7.1 Hz, OCH$_2$C<u>H</u>$_3$), 0.90 (9H, s, Si-C(C<u>H</u>$_3$)$_3$), 0.05 (6H, s, Si-(C<u>H</u>$_3$)$_2$).

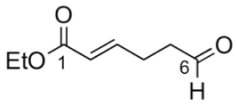
(*E*)-Ethyl 6-hydroxyhex-2-enoate[142]



To a solution of TBS ether **147** (2.00 g, 7.3 mmol) in MeOH/CH_2Cl_2 (1:4, 20.0 mL) at 0 ºC was added (±)-CSA (170 mg, 0.73 mmol). After 1.5 h, saturated $NaHCO_3$ (20.0 mL) solution and CH_2Cl_2 (20.0 mL) were added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by flash column chromatography (10% EtOAc/Hexanes) provided alcohol (1.13 g, 98%) as a colourless oil.

***R**f* 0.22 (20% EtOAc/Hexanes); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.97 (1H, dt, *J* = 15.6, 7.0, H-3), 5.84 (1H, dt, *J* = 15.6, 1.6 Hz, H-2), 4.18 (2H, q, *J* = 7.1 Hz, $OC\underline{H}_2CH_3$), 3.67 (2H, t, *J* = 6.4 Hz, H-6), 2.34-2.27 (2H, m, H-4), 1.77-1.68 (2H, m, H-5), 1.28 (3H, t, *J* = 7.1 Hz, $OCH_2C\underline{H}_3$).

(*E*)-Ethyl 6-oxohex-2-enoate (143)[95]

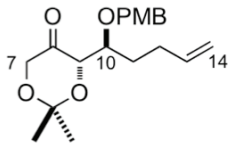


To a solution of oxalyl chloride (820 µL, 9.74 mmol) in CH_2Cl_2 (10.0 mL) at -78 ºC was slowly added DMSO (830 µL, 11.7 mmol). After 30 min, a solution of alcohol (768 mg, 4.87 mmol) in CH_2Cl_2 (10.0 mL) was added, dropwise. After 1 h, Et_3N (3.36 mL, 24.1 mmol) was added and the slurry was allowed to attain rt. After 1 h, a saturated NH_4Cl (20.0 mL) solution was added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic extracts were washed with H_2O (50 mL), brine (50 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by flash column chromatography (5% Et_2O/Pet. Ether) provided aldehyde **143** (660 mg, 87%) as a colourless oil.

***R**f* 0.31 (15% EtOAc/Hexanes); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.80 (1H, d, *J* = 1.0 Hz, H-6), 6.94 (1H, dt, *J* = 15.7, 6.6 Hz, H-3), 5.85 (1H, dt, *J* = 15.7, 1.5 Hz, H-2), 4.18 (2H, q,

J = 7.1 Hz, OC<u>H</u>$_2$CH$_3$), 2.67-2.62 (2H, m, H-4), 2.57-2.52 (2H, m, H-5), 1.28 (3H, t, *J* = 7.1 Hz, OCH$_2$C<u>H</u>$_3$).

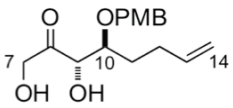
(*S*)-4-((*S*)-1-((4-Methoxybenzyl)oxy)pent-4-en-1-yl)-2,2-dimethyl-1,3-dioxan-5-one (148)



To a solution of alcohol **86** (0.84 g, 3.96 mmol) and PMBTCA (1.67 g, 5.94 mmol) in toluene (10.0 mL) at 0 ºC was added lanthanum(III)triflate (116 mg, 0.198 mmol). After 6 h, cold hexane (40.0 mL) was added and the precipitate was filtered. The resulting mixture was concentrated under reduced pressure and purified by flash column chromatography (10% EtOAc/Hexanes) to afford **148** (1.02 g, 77%) as a colourless oil.

***R*$_f$** 0.51 (20% EtOAc/Pet. Ether); $[\alpha]_D^{20}$ -9.3 (*c* 0.6, $CHCl_3$); **IR υ_{max}** (thin film/cm^{-1}) 3074, 3033, 2997, 2935, 2855, 2836, 1723, 1613, 1585, 1526, 1464, 1247, 1035, 821; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.27 (2H, d, *J* = 9.2 Hz, Ar-<u>H</u>), 6.87 (2H, d, *J* = 8.7 Hz, Ar-<u>H</u>), 5.77 (1H, dddd, *J* = 17.1, 10.1, 7.1, 6.2 Hz, H-13), 5.03-4.93 (2H, m, H-14), 4.61 (1H, d, *J* = 11.2 Hz, C<u>H</u>$_a$H$_b$Ar), 4.50 (1H, d, *J* = 11.2 Hz, CH$_a$<u>H</u>$_b$Ar), 4.42 (1H, dd, *J* = 3.1, 1.5 Hz, H-9), 4.23 (1H, dd, *J* = 16.7, 1.5 Hz, H-7a), 3.96 (1H, d, *J* = 16.7 Hz, H-7b), 3.88 (1H, dt, *J* = 9.4, 3.2 Hz, H-10), 3.80 (3H, s, Ar-OC<u>H</u>$_3$), 2.29-2.16 (1H, m, H-12a), 2.12-1.98 (1H, m, H-12b), 1.86 (1H, m, H-11a), 1.46 (3H, s, C-CH$_3$), 1.45 (3H, s, C-CH$_3$), 1.50-1.39 (1H, m, H-11b); **^{13}C NMR** (75 MHz; $CDCl_3$) δ 208.8, 159.7, 138.7, 130.7, 130.1, 129.8, 115.3, 114.2, 101.2, 76.3, 72.6, 67.5, 55.7, 30.4, 30.0, 24.7, 23.7; **HRMS** (ES$^+$) calcd. for $C_{19}H_{28}O_5$ $[M+H]^+$ 335.1853, found 335.1855.

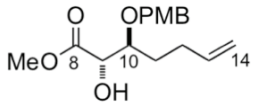
(3*S*,4*S*)-1,3-Dihydroxy-4-((4-methoxybenzyl)oxy)oct-7-en-2-one (150)



To a solution of acetonide **148** (280 mg, 0.854 mmol) in MeOH (8.5 mL) at rt was added *p*-toluenesulfonic acid monohydrate (16.0 mg, 0.085 mmol). After 3.5 h of stirring, Et_3N (0.36 mL, 2.56 mmol) was added and the mixture was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (30% EtOAc/Hexanes) to give diol **150** (234 mg, 92%) as a colourless oil.

***R*$_f$** 0.11 (30% EtOAc/Hexanes); $[\alpha]_D^{20}$ +3.7 (*c* 3.7, $CHCl_3$); **IR υ_{max}** (thin film/cm^{-1}) 3446, 2936, 2839, 1717, 1627, 1586, 1516, 1249, 1029, 823; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.24 (2H, d, *J* = 8.8 Hz, Ar-H), 6.90 (2H, d, *J* = 8.7 Hz, Ar-H), 5.77 (1H, dddd, *J* = 17.14, 10.16, 7.02, 6.23 Hz, H-13), 5.07-4.95 (2H, m, H-14), 4.54-4.31 (5H, m, CH_aH_bAr, H-7, H-9), 3.81 (3H, s, Ar-OCH_3), 3.67 (1H, ddd, *J* = 7.9, 4.9, 3.9 Hz, H-10), 3.04 (1H, dd, *J* = 5.8, 4.8 Hz, C7-OH), 2.83 (1H, d, *J* = 4.8 Hz, C9-OH), 2.25-2.06 (2H, m, H-12), 1.88-1.75 (1H, m, H-11a), 1.44-1.54 (1H, m, H-11b); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 211.8, 159.8, 137.9, 129.8, 129.4, 115.5, 114.2, 79.8, 75.9, 71.9, 67.8, 55.5, 29.2, 29.0; **HRMS** (ES^+) calcd. for $C_{16}H_{26}NO_5$ $[M+NH_4]^+$ 312.1805, found 312.1809.

(2*S*,3*S*)-Methyl 2-hydroxy-3-((4-methoxybenzyl)oxy)hept-6-enoate (149)



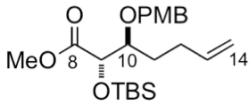
To a solution of diol **150** (190 mg, 0.645 mmol) in THF/H_2O (2:1, 20.0 mL, 0.033 M), at rt was added H_5IO_6 (220 mg, 0.968 mmol). After 24 h, Et_2O (20.0 mL) was added and the layers were separated and the aqueous phase was extracted with Et_2O (3 × 30 mL). The combined organic extracts were washed with water (20 mL), brine (20 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure.

To a suspension of the resulting residue and K_2CO_3 (110 mg, 0.774 mmol) in DMF (8.0 mL) at rt was added MeI (50 μL, 0.774 mmol). After 1 h, water (10.0 mL) was added, and the reaction mixture was extracted with Et_2O (3 × 30 mL). The combined organic layers

were washed with water (20 mL), brine (20 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc/Hexanes) to give methyl ester **149** (120 mg, 64%).

R_f 0.8 (30% EtOAc/Hexanes); $[\alpha]_D^{20}$ -2.5 (*c* 2.5 $CHCl_3$); **IR** υ_{max} (thin film/cm^{-1}) 3480, 2999, 2953, 2838, 1739, 1613, 1520, 1441, 1249, 1174, 1095, 1034, 821; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.26 (2H, d, *J* = 8.8 Hz, Ar-H), 6.88 (2H, d, *J* = 8.8 Hz, Ar-H), 5.76 (1H, dddd, *J* = 17.0, 10.4, 6.8, 6.4 Hz, H-13), 5.03-4.94 (2H, m, H-14), 4.61 (1H, d, *J* = 11.3 Hz, CH_aH_bAr), 4.51 (1H, d, *J* = 11.3 Hz, CH_aH_bAr), 4.39 (1H, dd, *J* = 5.5, 3.0 Hz, H-9), 3.81 (3H, s, Ar-OCH_3), 3.80 (3H, s, C8-OCH_3), 3.71 (1H, ddd, *J* = 9.0, 4.0, 3.0 Hz, H-10), 2.85 (1H, d, *J* = 5.6 Hz, C9-OH), 2.27-2.14 (1H, m, H-12a), 2.13-1.99 (1H, m, H-12b), 1.89-1.74 (1H, m, H-11a), 1.52-1.40 (1H, m, H-11b); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.2, 159.4, 138.1, 130.3, 129.7, 115.2, 114.0, 79.9, 72.6, 72.3, 55.4, 52.7, 29.9, 29.6; **HRMS** (ES^+) calcd. for $C_{16}H_{26}NO_5$ $[M+NH_4]^+$ 312.1805, found 312.1808.

(2*S*,3*S*)-Methyl-2-((*tert*-butyldimethylsilyl)oxy)-3-((4-methoxybenzyl)oxy)hept-6-enoate (153)

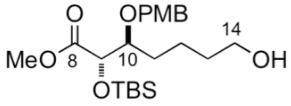


To a solution of alcohol **149** (140 mg, 0.476 mmol) in CH_2Cl_2 (5.0 mL) at -78 ºC was added 2,6-lutidine (111 µL, 0.952 mmol) and TBSOTf (164 µL, 0.714 mmol). After 2 h, saturated NH_4Cl (5.0 mL) solution and CH_2Cl_2 (5.0 mL) were added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by flash column chromatography (5-10% EtOAc/Hexanes) provided TBS ether **153** (190 mg, 98%) as a colourless oil.

R_f 0.16 (20% EtOAc/Hexanes); $[\alpha]_D^{20}$ -10.2 (*c* 0.5, $CHCl_3$); **IR** υ_{max} (thin film/cm^{-1}) 2954, 2930, 2858, 1756, 1730, 1514, 1275, 1153, 1122, 837, 779; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.24 (2H, d, *J* = 8.8 Hz, Ar-H), 6.86 (2H, d, *J* = 8.8 Hz, Ar-H), 5.82-5.72 (1H, m, H-13), 5.01-4.92 (2H, m, H-14), 4.57 (1H, d, *J* = 11.0 Hz, CH_aH_bAr), 4.44 (1H, d, *J* = 11.0 Hz, CH_aH_bAr), 4.30 (1H, d, *J* = 4.6 Hz, H-9), 3.80 (3H, s, Ar-OCH_3), 3.72 (3H, s, C8-OCH_3), 3.68 (1H, ddd, *J* = 8.3, 4.6, 3.7 Hz, H-10), 2.24-2.14 (1H, m, H-12a), 2.12-2.02 (1H, m,

H-12b), 1.80-1.70 (1H, m, H-11a), 1.65-1.56 (1H, m, H-11b), 0.91 (9H, s, Si-C(C<u>H</u>$_3$)$_3$), 0.07 (6H, s, Si-(C<u>H</u>$_3$)$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.9, 159.3, 138.5, 130.6, 129.7, 114.9, 113.8, 80.5, 74.3, 72.2, 55.4, 51.9, 30.0, 29.6, 25.8, 18.4, -4.97, -5.08; **HRMS** (ES^+) calcd. for $C_{22}H_{40}NO_5Si$ $[M+NH_4]^+$ 426.2670, found 426.2667.

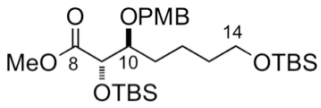
(2*S*,3*S*)-Methyl-2-((*tert*-butyldimethylsilyl)oxy)-7-hydroxy-3-((4-methoxybenzyl)oxy)-heptanoate (154)



To a solution of thexylBH_2 in THF (4.0 mL, 0.5 M, 2.0 mmol) at 0 ^oC was added olefin **153** (200 mg, 0.489 mmol) in THF (2.0 mL) dropwise. After 1h NaOH (2.0 mL, 10% w/v) and H_2O_2 (2 mL, 30% v/v) were added. The mixture was stirred for 30 min and the aqueous layer was saturated with anhydrous K_2CO_3. The organics were extracted with CH_2Cl_2 (3 × 10 mL), washed with brine (30 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc/Hexane) to give alcohol **154** (200 mg, 96%) as a colourless oil.

***R*$_f$** 0.38 (20% EtOAc/Hexane); $[\alpha]_D^{20}$ -11.8 (*c* 0.8, $CHCl_3$); **IR υ_{max}** (thin film/cm^{-1}) 3446, 2951, 2930, 2857, 1750, 1514, 1247, 1207, 1155, 1035, 837, 779; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.23 (2H, d, *J* = 8.7 Hz, Ar-<u>H</u>), 6.85 (2H, d, *J* = 8.7 Hz, Ar-<u>H</u>), 4.57 (1H, d, *J* = 11.1 Hz, C<u>H</u>$_a$H$_b$Ar), 4.43 (1H, d, *J* = 11.1 Hz, CH$_a$<u>H</u>$_b$Ar), 4.30 (1H, d, *J* = 4.5 Hz, H-9), 3.79 (3H, s, Ar-OC<u>H</u>$_3$), 3.71 (3H, s, C8-OC<u>H</u>$_3$), 3.67-3.63 (1H, m, H-10), 3.59 (2H, t, *J* = 6.3 Hz, H-14), 1.72-1.60 (2H, m, H-11a, H-13a), 1.57-1.46 (2H, m, H-11b, H-13b), 1.39-1.29 (2H, m, H-12), 0.90 (9H, s, Si-C(C<u>H</u>$_3$)$_3$), 0.06 (6H, s, 2 × Si-C<u>H</u>$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.0, 159.3, 130.5, 129.7, 113.8, 80.9, 74.3, 72.3, 63.0, 55.4, 52.0, 32.8, 30.4, 25.8, 21.6, 18.4, -4.95, -5.08; **HRMS** (ES^+) calcd. for $C_{22}H_{42}NO_6Si$ $[M+NH_4]^+$ 444.2776, found 444.2779.

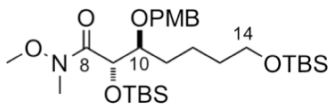
(2*S*,3*S*)-Methyl-2,7-bis((*tert*-butyldimethylsilyl)oxy)-3-((4-methoxybenzyl)oxy)-heptanoate (155)



To a solution of TBSCl (85.0 mg, 0.564 mmol) and imidazole (40.0 mg, 0.587 mmol) in DMF (1.0 mL) at 0 ºC was added a solution of alcohol **154** (200 mg, 0.468 mmol) in DMF (2.0 mL). After 12 h, a saturated NH_4Cl (5.0 mL) solution was added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were washed with H_2O (10 mL), brine (10 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by flash column chromatography (2% EtOAc/Hexanes) provided bis-TBS-ether **155** (230 mg, 92%) as a colourless oil.

R_f 0.72 (20% EtOAc/Hexane); $[\alpha]_D^{20}$ -11.8 (*c* 0.8, $CHCl_3$); **IR υ_{max}** (thin film/cm^{-1}) 2951, 2929, 2896, 2857, 1756, 1514, 1249, 1203, 1150, 1103, 820, 776; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.23 (2H, d, *J* = 8.7 Hz, Ar-H), 6.85 (2H, d, *J* = 8.7 Hz, Ar-H), 4.55 (1H, d, *J* = 11.0 Hz, CH_aH_bAr), 4.44 (1H, d, *J* = 11.0 Hz, CH_aH_bAr), 4.28 (1H, d, *J* = 4.8 Hz, H-9), 3.79 (3H, s, Ar-OCH_3), 3.71 (3H, s, C8-OCH_3), 3.65 (1H, ddd, *J* = 8.0, 4.6, 3.5 Hz, H-10), 3.57 (2H, t, *J* = 6.3 Hz, H-14), 1.68-1.57 (1H, m, H-11a), 1.52-1.44 (3H, m, H-11b, H-12), 1.37-1.25 (2H, m, H-13), 0.90 (9H, s, Si-$C(CH_3)_3$), 0.89 (9H, s, Si-$C(CH_3)_3$), 0.06 (6H, s, 2 × Si-CH_3), 0.04 (6H, s, 2 × Si-CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.0, 159.3, 130.7, 129.7, 113.8, 81.2, 74.4, 72.3, 63.2, 55.4, 51.9, 33.1, 30.6, 26.1, 25.8, 21.8, 18.5, 18.4, -4.9, -5.08, -5.12; **HRMS** (ES^+) calcd. for $C_{28}H_{56}NO_6Si_2$ $[M+NH_4]^+$ 558.3641, found 558.3635.

(2*S*,3*S*)-2,7-Bis((*tert*-butyldimethylsilyl)oxy)-*N*-methoxy-3-((4-methoxybenzyl)oxy)-*N*-methylheptanamide (156)

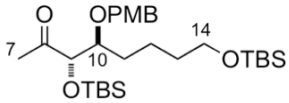


To a solution of methylester **155** (0.851 g, 1.57 mmol) and *N*,*O*-dimethyl hydroxylamine hydrochloride (0.228 g, 2.35 mmol) in THF (50.0 mL) at -30 ºC was slowly added *i*-PrMgCl (3.54 mL, 2M soln. in THF, 7.08 mmol). The reaction mixture was allowed to

attain 0 ºC. After 6 h a saturated NH_4Cl (50.0 mL) solution was added and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 30 mL) and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by flash column chromatography (10% EtOAc/Hexanes) provided Weinreb amide **156** (870 mg, 97%) as a colourless oil.

R_f 0.57 (20% EtOAc/Hexane); $[\alpha]_D^{20}$ -6.6 (*c* 0.6, $CHCl_3$); **IR υ_{max}** (thin film/cm^{-1}) 2950, 2928, 2856, 1670, 1514, 1250, 1203, 1148, 1103, 823, 775; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.19 (2H, d, *J* = 8.8 Hz, Ar-H), 6.82 (2H, d, *J* = 8.8 Hz, Ar-H), 4.63-4.51 (1H, m, H-9), 4.43 (1H, d, *J* = 10.7 Hz, CH_aH_bAr), 4.41 (1H, d, *J* = 10.7 Hz, CH_aH_bAr), 3.78 (3H, s, Ar-OCH_3), 3.70 (1H, td, *J* = 7.4, 3.2 Hz, H-10), 3.62-3.59 (5H, m, N-OCH_3, H-14), 3.21 (3H, s, N-CH_3), 1.79-1.65 (1H, m, H-11a), 1.62-1.45 (4H, m, H-11b, H-12, H-13a), 1.44-1.37 (1H, m, H-13b), 0.89 (9H, s, Si-C(CH_3)$_3$), 0.88 (9H, s, Si-C(CH_3)$_3$), 0.06 (3H, s, Si-CH_3), 0.05 (3H, s, Si-CH_3), 0.04 (6H, s, 2 × Si-CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.2, 130.9, 129.7, 113.7, 80.8, 73.0, 63.4, 55.4, 33.3, 31.1, 26.1, 25.9, 21.4, 18.5, 18.3, -4.7, -4.97, -5.11; **HRMS** (ES^+) calcd. for $C_{29}H_{56}O_6NSi_2$ $[M+H]^+$ 570.3641, found 570.3638.

(3*S*,4*S*)-3,8-Bis((*tert*-butyldimethylsilyl)oxy)-4-((4-methoxybenzyl)oxy)octan-2-one (144)

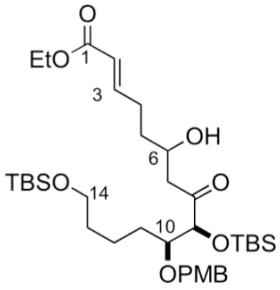


To a solution of Weinreb amide **156** (848 mg, 1.56 mmol) in THF (20.0 mL) at 0 ºC was added MeMgBr (2.1 mL, 3.0 M soln. in THF, 6.25 mmol). The reaction mixture was stirred at 0 ºC for 1 h and quenched with saturated NH_4Cl (20.0 mL) solution. The reaction mixture was allowed to warm to rt and H_2O (5.0 mL) was added to dissolve the precipitate, and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 20 mL) and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification of the residue by flash column chromatography (5% EtOAc/Hexanes) afforded product **144** (785 mg, 96%) as a colourless oil.

R_f 0.75 (20% EtOAc/Hexanes); $[\alpha]_D^{20}$ -9.7 (*c* 0.8, $CHCl_3$); **IR υ_{max}** (thin film/cm^{-1}) 2954, 2856, 1714, 1514, 1249, 1209, 1149, 1102, 837, 776; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.25 (2H, d, *J* = 8.6 Hz, Ar-H), 6.86 (2H, d, *J* = 8.5 Hz, Ar-H), 4.61 (1H, d, *J* = 11.2 Hz,

C$\underline{H}_a$H$_b$Ar), 4.45 (1H, d, *J* = 11.1 Hz, CH$_a\underline{H}_b$Ar), 4.10 (1H, d, *J* = 3.5 Hz, H-9), 3.80 (3H, s, Ar-OC$\underline{H}_3$), 3.57 (3H, dd, *J* = 7.9, 4.5 Hz, H-10, H-14), 2.19 (3H, s, H-7), 1.64-1.56 (1H, m, H-11a), 1.50-1.42 (3H, m, H-11b, H-13), 1.35-1.22 (2H, m, H-12), 0.93 (9H, s, Si-C(C$\underline{H}_3$)$_3$), 0.88 (9H, s, Si-C(C$\underline{H}_3$)$_3$), 0.08 (3H, s, Si-C$\underline{H}_3$), 0.05 (3H, s, Si-C$\underline{H}_3$), 0.03 (6H, s, 2 × Si-C$\underline{H}_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 211.8, 159.3, 130.5, 129.6, 113.8, 81.8, 80.7, 72.4, 63.2, 55.4, 33.0, 30.4, 27.4, 26.1, 25.9, 22.0, 18.5, 18.3, -4.6, -5.0, -5.1; **HRMS** (ES$^+$) calcd. for $C_{28}H_{56}NO_5Si_2$ $[M+NH_4]^+$ 542.3692, found 542.3687.

(9*S*,10*S*,*E*)-Ethyl-9,14-bis((*tert*-butyldimethylsilyl)oxy)-6-hydroxy-10-((4-methoxybenzyl)oxy)-8-oxotetradec-2-enoate (157)

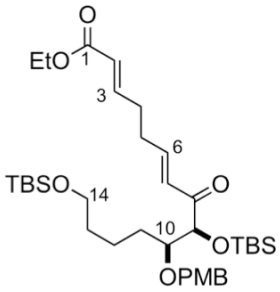


To a stirred solution of ketone **144** (320 mg, 0.610 mmol) in Et_2O (15.0 mL) at -78 ºC was added dicyclohexylboron chloride (240 µL, 1.09 mmol) and Et_3N (170 µL, 1.21 mmol) and the reaction mixture was stirred for 0.5 h. Aldehyde **143** (143 mg, 0.91 mmol) in Et_2O (5.0 mL) was then added. After 2 h the reaction mixture was diluted with MeOH (3.0 mL), phosphate buffer pH 7 (3.0 mL) and H_2O_2 (3 mL, 30% v/v). The biphasic mixture was allowed to warm to RT and stirred vigorously for 10 min. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried ($NaSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (10% EtOAc/Hexanes) gave aldol adduct **157** (373 mg, 90%) as an inconsequential 1.6 : 1 mixture of diastereoisomers.

***R**$_f$* 0.48 (20% EtOAc/Hexanes); **IR υ_{max}** (thin film/cm^{-1}) 3513, 2954, 2856, 1720, 1653, 1514, 1250, 1172, 1100, 1040, 837, 778; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.22 (2H, d, *J* = 8.7 Hz, Ar-$\underline{H}$), 6.98-6.87 (2H, m, H-3), 6.84 (2H, d, *J* = 8.7 Hz, Ar-$\underline{H}$), 5.77-5.87 (2H, m, H-2), 4.57 (1H, d, *J* = 11.1 Hz, C$\underline{H}_a$H$_b$Ar), 4.46 (1H, d, *J* = 11.1 Hz, CH$_a\underline{H}_b$Ar), 4.17 (2H, q, *J* = 7.1 Hz, OC$\underline{H}_2$CH$_3$), 4.08 (2H, d, *J* = 3.9 Hz, H-9), 4.02-3.91 (1H, m, H-6), 3.79 (3H, s, Ar-OC$\underline{H}_3$), 3.59-3.54 (3H, m, H-10, H-14), 3.06 (1H, d, *J* = 3.3 Hz, C6-O$\underline{H}$), 2.81-2.67

(2H, m, H-7), 2.64-2.48 (2H, m, H-4), 2.32-2.19 (4H, m, H-5, H-11), 1.61-1.38 (4H, m, H-12, H-13), 1.27 (3H, t, J = 7.1 Hz, $OCH_2C\underline{H}_3$), 0.92 (9H, s, Si-C($C\underline{H}_3$)$_3$), 0.88 (9H, s, Si-C($C\underline{H}_3$)$_3$), 0.07 (6H, s, 2 × Si-$C\underline{H}_3$), 0.02 (6H, s, 2 × Si-$C\underline{H}_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 214.3, 166.7, 159.4, 148.7, 130.2, 129.7, 121.8, 113.9, 81.9, 80.5, 72.5, 66.9, 63.1, 60.3, 55.4, 45.9, 34.9, 32.9, 30.3, 28.3, 26.1, 25.9, 21.9, 18.5, 18.2, 14.4, -4.6, -4.9, -5.1; **HRMS** (ES^+) calcd. for $C_{36}H_{68}NO_8Si_2$ $[M+NH_4]^+$ 698.4478, found 698.4477.

(2*E*,6*E*,9*S*,10*S*)-Ethyl-9,14-bis((*tert*-butyldimethylsilyl)oxy)-10-((4-methoxybenzyl)-oxy)-8-oxotetradeca-2,6-dienoate (142)



Method A

To a stirred solution of aldol product **157** (350 mg, 0.514 mmol) in CH_2Cl_2 (5.0 mL) at -10 ºC was added a solution of Martin's sulfurane (518 mg, 0.771 mmol) in CH_2Cl_2 (5.0 mL). The resulting pale yellow mixture was stirred for 1 h and the residual solvent was removed under reduced pressure to yield the crude product as a pale yellow oil. Purification by flash column chromatography (5-10% EtOAc/Hexanes) furnished the compound **142** as a colourless oil (320 mg, 95%).

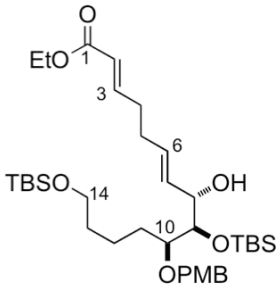
Method B

To a solution of aldol product **157** (80 mg, 0.117 mmol) in CH_2Cl_2 (2.0 mL) at 0 ºC was added Et_3N (40 µL, 0.292 mmol) and mesyl chloride (20 µL, 0.258 mmol) and the reaction mixture was allowed to attained rt, DBU (90 µL, 0.585 mmol) was then added and the reaction was stirred for 16 h before quenching with saturated NH_4Cl (5.0 mL) solution. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting residue was purified by

flash column chromatography (5-10% EtOAc/Hexanes) to give product **142** (46.0 mg, 62%) as a colourless oil.

R_f 0.65 (20% EtOAc/Hexane); $[\alpha]_D^{20}$ -10.0 (*c* 3.0, $CHCl_3$); **IR** υ_{max} (thin film/cm^{-1}) 2954, 2929, 2856, 1724, 1514, 1250, 1172, 1098, 1040, 837, 775; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.23 (2H, d, *J* = 8.5 Hz, Ar-H), 6.93 (2H, dt, *J* = 15.7, 6.4 Hz, H-3, H-6), 6.85 (2H, d, *J* = 8.6 Hz, Ar-H), 6.66 (1H, d, *J* = 15.8 Hz, H-7), 5.84 (1H, d, *J* = 15.7 Hz, H-2), 4.57 (1H, d, *J* = 11.1 Hz, CH_aH_bAr), 4.44 (1H, d, *J* = 11.2 Hz, CH_aH_bAr), 4.23 (1H, d, *J* = 4.0 Hz, H-9), 4.18 (2H, q, *J* = 7.1 Hz, OCH_2CH_3), 3.80 (3H, s, Ar-OCH_3), 3.56 (3H, m, H-10, H-14), 2.41-2.30 (4H, m, H-4, H-5), 1.65-1.54 (1H, m, H-11a), 1.52-1.41 (4H, m, H-11b, H-12, H-13a), 1.28 (4H, t, *J* = 7.1 Hz, OCH_2CH_3, H-13b), 0.92 (9H, s, Si-$C(CH_3)_3$), 0.89 (9H, s, Si-$C(CH_3)_3$), 0.07 (3H, s, Si-CH_3), 0.03 (6H, s, 2 × Si-CH_3), 0.02 (3H, s, Si-CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.7, 166.4, 159.2, 147.1, 145.8, 130.5, 129.7, 126.5, 122.4, 113.8, 81.6, 79.9, 72.3, 63.2, 60.4, 55.4, 33.0, 31.0, 30.5, 26.1, 25.9, 22.0, 18.5, 18.3, 14.4, -4.7, -4.9, -5.1; **HRMS** (ES^+) calcd. for $C_{36}H_{66}NO_7Si_2$ $[M+NH_4]^+$ 680.4372, found 680.4370.

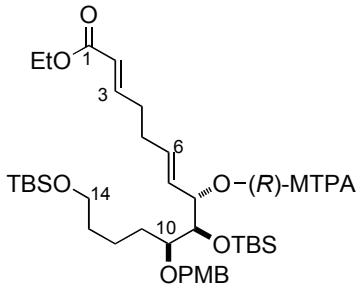
(2*E*,6*E*,8*S*,9*R*,10*S*)-9,14-bis((*tert*-butyldimethylsilyl)oxy)-8-hydroxy-10-((4-methoxybenzyl)oxy)tetradeca-2,6-dienoate (163)



To a solution of enone **142** (480 mg, 0.724 mmol) in MeOH (20.0 mL) was added $CeCl_3•7H_2O$ (405 mg, 1.08 mmol) before reaction mixture was cooled to -78 ºC and $NaBH_4$ (33 mg, 0.868 mmol) was added. The reaction was stirred for 1h before quenching with saturated $NaHCO_3$ (20.0 mL) solution and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 10 mL) and the combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (10% EtOAc/Hexanes) to give allylic alcohol **163** (445 mg, 90%) as a colourless oil.

***R**f* 0.56 (20% EtOAc/Hexane); $[\alpha]_D^{20}$ -4.1 (*c* 1.1, $CHCl_3$); **IR** υ_{max} (thin film/cm^{-1}) 3251, 2926, 2847, 1810, 1719, 1513, 1302, 1250, 1205, 1148, 833, 777; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.24 (2H, d, *J* = 8.6 Hz, Ar-H), 6.97 (1H, dt, *J* = 15.6, 6.6 Hz, H-3), 6.86 (2H, d, *J* = 8.7 Hz, Ar-H), 5.84 (1H, dt, *J* = 15.6, 1.4 Hz, H-2), 5.68-5.74 (1H, m, H-6), 5.54 (1H, dd, *J* = 15.5, 5.7 Hz, H-7), 4.49 (1H, d, *J* = 10.7 Hz, CH_aH_bAr), 4.44 (1H, d, *J* = 10.8 Hz, CH_aH_bAr), 4.17 (2H, q, *J* = 7.1 Hz, OCH_2CH_3), 4.10-4.14 (1H, m, H-8), 3.79 (3H, s, Ar-OCH_3), 3.66 (1H, dd, *J* = 4.9, 4.2 Hz, H-9), 3.60 (2H, t, *J* = 6.2 Hz, H-14), 3.48 (1H, m, H-10), 3.25 (1H, d, *J* = 6.2 Hz, C8-OH), 2.31-2.27 (2H, m, H-4), 2.24-2.21 (2H, m, H-5), 1.64-1.54 (2H, m, H-11), 1.54-1.45 (3H, m, H-13, H-12a), 1.41-1.32 (1H, m, H-12b), 1.28 (3H, t, *J* = 7.1 Hz, OCH_2CH_3), 0.90 (9H, s, Si-C(CH_3)$_3$), 0.89 (9H, s, Si-C(CH_3)$_3$), 0.09 (3H, s, Si-CH_3), 0.07 (3H, s, Si-CH_3), 0.05 (6H, s, 2 × Si-CH_3); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.7, 159.4, 148.4, 131.1, 130.8, 130.3, 129.7, 121.9, 113.9, 81.1, 75.4, 73.3, 72.2, 63.3, 60.3, 55.4, 33.2, 31.9, 31.0, 30.2, 26.13, 26.1, 21.6, 18.5, 18.3, 14.4, -4.0, -4.3, -5.1; **HRMS** (ES^+) calcd. for $C_{36}H_{66}NO_7Si_2$ $[M+NH_4]^+$ 680.4372, found 680.4370.

***(R)*-Mosher ester of 163 (164)**

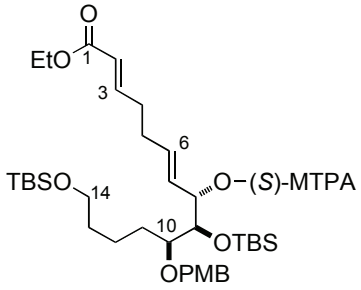


To a stirred mixture of alcohol **163** (10.0 mg, 15 μmol), DCC (13.0 mg, 61 μmol) and DMAP (3.7 mg, 31 μmol) in CH_2Cl_2 (1.0 mL) at rt was added (+)-(*R*)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (7.0 mg, 30 μmol) in one portion. After 16 h, the crude reaction mixture was purified directly by flash column chromatography (5% EtOAc/Hexanes) to give (*R*)-MTPA ester **164** (12.0 mg, 92%) as a colourless oil.

***R**f* 0.66 (20% EtOAc/Hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.56-7.54 (2H, m, Ph-H), 7.36 (3H, m, Ph-H), 7.21 (2H, d, *J* = 8.6 Hz, Ar-H), 6.92 (1H, dt, *J* = 15.7, 6.3 Hz, H-3), 6.85 (2H, d, *J* = 8.6 Hz, Ar-H), 5.81 (1H, dd, *J* = 15.8, 1.3 Hz, H-2), 5.82-5.74 (1H, m, H-6), 5.55 (1H, d, *J* = 1.5 Hz, H-8), 5.58-5.50 (1H, m, H-7), 4.27 (1H, d, *J* = 10.7 Hz, CH_aH_bAr), 4.22 (1H, d, *J* = 10.7 Hz, CH_aH_bAr), 4.17 (2H, q, *J* = 7.1 Hz, OCH_2CH_3), 3.80

(3H, s, Ar-OC$\underline{H}_3$), 3.76 (1H, td, *J* = 3.3, 1.7 Hz, H-9), 3.57-3.54 (2H, m, H-14), 3.54 (3H, s, OC$\underline{H}_3$), 3.25 (1H, q, *J* = 5.3 Hz, H-10), 2.26-2.18 (4H, m, H-4, H-5), 1.52-1.45 (2 H, m, H-11), 1.46-1.39 (2H, m, H-13), 1.27 (3H, t, *J* = 7.1 Hz, $OCH_2C\underline{H}_3$), 1.20-1.26 (2H, m, H-12), 0.89 (9H, s, Si-C(C$\underline{H}_3$)$_3$), 0.85 (9H, s, Si-C(C$\underline{H}_3$)$_3$), 0.04 (3H, s, Si-C$\underline{H}_3$), 0.04 (6H, s, 2 × Si-C$\underline{H}_3$), 0.00 (3H, s, Si-C$\underline{H}_3$).

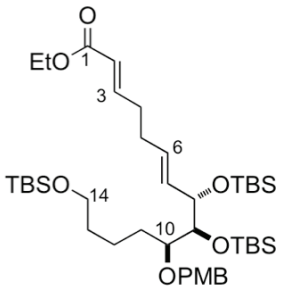
***(S)*-Mosher ester of 163 (165)**



To a stirred mixture of alcohol **163** (5.0 mg, 7.7 μmol), DCC (6.3 mg, 31 μmol) and DMAP (1.8 mg, 15 μmol) in CH_2Cl_2 (1.0 mL) at rt was added (+)-(*S*)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (3.5 mg, 15 μmol) in one portion. After 16 h, the crude reaction mixture was purified directly by flash column chromatography (5% EtOAc/Hexanes) to give (*S*)-MTPA ester **165** (5.0 mg, 75%).

***R*$_f$** 0.66 (20% EtOAc/Hexanes); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.54 (2H, d, *J* = 8.3 Hz, Ph-$\underline{H}$), 7.40-7.34 (3H, m, Ph-$\underline{H}$), 7.22 (2H, d, *J* = 8.7 Hz, Ar-$\underline{H}$), 6.91 (1H, dt, *J* = 15.7, 6.5 Hz, H-3), 6.84 (2H, d, *J* = 8.7 Hz, Ar-$\underline{H}$), 5.81 (1H, d, *J* = 15.7 Hz, H-2), 5.67 (1H, dt, *J* = 15.4, 6.3 Hz, H-6), 5.60 (1H, dd, *J* = 7.5, 2.9 Hz, H-8), 5.44 (1H, dd, *J* = 16.0, 7.4 Hz, H-7), 4.31 (1H, d, *J* = 10.7 Hz, C$\underline{H}_a$H$_b$Ar), 4.29 (1H, d, *J* = 10.7 Hz, CH$_a\underline{H}_b$Ar), 4.17 (2H, q, *J* = 7.1 Hz, OC$\underline{H}_2$CH$_3$), 3.79 (3H, s, Ar-OC$\underline{H}_3$), 3.79-3.76 (1H, m, H-9), 3.57 (3H, t, *J* = 6.2 Hz, H-14), 3.50 (3H, s, OC$\underline{H}_3$), 3.31 (1H, td, *J* = 5.9, 3.5 Hz, H-10), 2.24-2.19 (2H, m, H-4), 2.19-2.13 (2H, m, H-5), 1.51-1.42 (2H, m, H-11), 1.27 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.21-1.27 (4H, m, H-12, H-13), 0.89 (9H, s, Si-C(C$\underline{H}_3$)$_3$), 0.85 (9H, s, Si-C(C$\underline{H}_3$)$_3$), 0.05 (3H, s, Si-(C$\underline{H}_3$)$_2$), 0.04 (6H, s, 2 × Si-C$\underline{H}_3$), 0.02 (3H, s, Si-(C$\underline{H}_3$)$_2$).

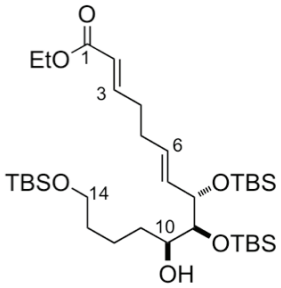
(2*E*,6*E*,8*S*,9*S*,10*S*)-Ethyl-8,9,14-tris((*tert*-butyldimethylsilyl)oxy)-10-((4-methoxy-benzyl)oxy)tetradeca-2,6-dienoate (166)



To a solution of alcohol **163** (450 mg, 0.677 mmol) in CH_2Cl_2 (10.0 mL) at -78 ºC was added 2,6-lutidine (160 µL, 1.35 mmol) and TBSOTf (233 µL, 1.01 mmol). After 4 h, saturated NH_4Cl (20.0 mL) solution and CH_2Cl_2 (20.0 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by flash column chromatography (5% EtOAc/Hexanes) provided TBS ether **166** (460 g, 87%) as a colourless oil.

R_f 0.9 (20% EtOAc/Hexanes); $[\alpha]_D^{20}$ -16.3 (*c* 1.4, $CHCl_3$); **IR υ_{max}** (thin film/cm^{-1}) 2952, 2933, 2893, 2858, 1723, 1512, 1466, 1252, 1101, 1043, 836, 777; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.25 (2H, d, *J* = 8.7 Hz, Ar-H), 6.95 (1 H, dt, *J* = 15.7, 6.5 Hz, H-3), 6.85 (2H, d, *J* = 8.8 Hz, Ar-H), 5.82 (1H, dt, *J* = 15.7, 1.4 Hz, H-2), 5.58-5.56 (2H, m, H-6, H-7), 4.52 (1H, d, *J* = 11.1 Hz, CH_aH_bAr), 4.25 (1H, d, *J* = 11.1 Hz, CH_aH_bAr), 4.18 (2H, q, *J* = 7.1 Hz, OCH_2CH_3), 4.11-4.08 (1H, m, H-8), 3.87 (1H, dd, *J* = 4.9, 1.5 Hz, H-9), 3.80 (3H, s, Ar-OCH_3), 3.55 (2H, t, *J* = 6.5 Hz, H-14), 3.45-3.42 (1H, m, H-10), 2.28-2.19 (4H, m, H-4, H-5), 1.47-1.42 (4H, m, H-11, H-13), 1.28 (3H, t, *J* = 7.1 Hz, OCH_2CH_3), 1.26-1.16 (2H, m, H-12), 0.91 (9H, s, Si-$C(CH_3)_3$), 0.90 (9H, s, Si-$C(CH_3)_3$), 0.88 (9H, s, Si-$C(CH_3)_3$), 0.07 (3H, s, Si-CH_3), 0.07 (3H, s, Si-CH_3), 0.06 (3H, s, Si-CH_3), 0.04 (3H, s, Si-CH_3), 0.03 (6H, s, 2 × Si-CH_3); **^{13}C NMR** (75 MHz; $CDCl_3$) δ 166.7, 159.0, 148.4, 131.4, 130.9, 129.4, 128.9, 121.9, 113.7, 79.7, 74.7, 71.3, 63.6, 60.3, 55.4, 33.3, 32.1, 31.0, 30.9, 26.14, 26.11, 26.06, 22.7, 18.5, 18.4, 18.3, 14.4, -4.2, -4.3, -4.5, -4.6, -5.09, -5.11; **HRMS** (ES^+) calcd. for $C_{42}H_{82}NO_7Si_3$ $[M+NH_4]^+$ 796.5394, found 796.5394.

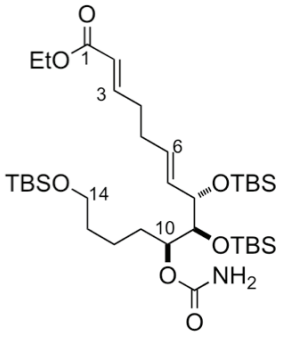
(2*E*,6*E*,8*S*,9*S*,10*S*)-Ethyl 8,9,14-tris((*tert*-butyldimethylsilyl)oxy)-10-hydroxytetradeca-2,6-dienoate (167)



To a solution of PMB ether **166** (150 mg, 0.192 mmol) in CH_2Cl_2 (2.0 mL) and phosphate buffer pH 7 (0.1 mL) at 0 ^oC was added DDQ (65.0 mg, 0.288 mmol). The reaction mixture was stirred for 1 h before quenching with saturated $NaHCO_3$ (5.0 mL) solution and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by flash column chromatography (5% EtOAc/Hexanes) provided alcohol **167** (110 mg, 88 % yield) as a colourless oil.

R_f 0.76 (15% EtOAc/Hexanes); $[\alpha]_D^{20}$ -24.4 (*c* 1.0, $CHCl_3$); **IR υ_{max}** (thin film/cm^{-1}) 3418, 2921, 2847, 1719, 1277, 1126, 835, 766; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.00-6.90 (1H, m, H-3), 5.86-5.80 (1H, m, H-2), 5.69-5.67 (2H, m, H-6, H-7), 4.31-4.27 (1H, m, H-8), 4.17 (2H, q, *J* = 7.1 Hz, $OC\underline{H}_2CH_3$), 3.91 (1H, s, C10-O<u>H</u>), 3.63-3.57 (3H, m, H-10, H-14), 3.40 (1H, dd, *J* = 8.5, 4.2 Hz, H-9), 2.31-2.26 (4H, m, H-4, H-5), 1.57-1.51 (4H, m, H-12, H-13), 1.35-1.27 (2H, m, H-11), 1.27 (3H, t, *J* = 7.1 Hz, $OCH_2C\underline{H}_3$), 0.90 (9H, s, Si-$C(CH_3)_3$), 0.88 (9H, s, Si-$C(CH_3)_3$), 0.87 (9H, s, Si-$C(CH_3)_3$), 0.09 (3H, s, Si-CH_3), 0.08 (6H, s, 2 × Si-$C\underline{H}_3$), 0.05 (3H, s, Si-CH_3), 0.03 (6H, s, 2 × Si-$C\underline{H}_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.7, 148.3, 130.8, 128.6, 122.0, 76.7, 75.5, 72.6, 63.6, 60.3, 33.8, 33.3, 32.1, 30.9, 26.2, 25.95, 25.91, 21.5, 18.6, 18.2, 18.1, 14.4, -4.0, -4.5, -4.6, -4.9, -5.1; **HRMS** (ES^+) calcd. for $C_{34}H_{74}O_6NSi_3$ $[M+NH_4]^+$ 676.4818, found 676.4802.

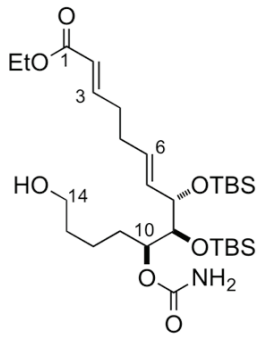
(2*E*,6*E*,8*S*,9*S*,10*S*)-Ethyl 8,9,14-tris((*tert*-butyldimethylsilyl)oxy)-10-(carbamoyloxy)-tetradeca-2,6-dienoate (168)



To a stirred solution of alcohol **167** (45.0 mg, 0.683 μmol) in CH_2Cl_2 (4.0 mL) was added trichloroacetyl isocyanate (16.3 μL, 0.136 mmol) at 0 ºC and the reaction was stirred at rt for 1 h. CH_2Cl_2 (2.0 mL) and an excess amount of Al_2O_3 was added and the resulting suspension was stirred overnight. The suspension was filtered, concentrated under reduced pressure and purified by flash column chromatography (10-20% EtOAc/Hexanes) to give carbamate **168** (34.0 mg, 72%) as a colourless oil.

R_f 0.29 (10% EtOAc/Hexanes); $[\alpha]_D^{20}$ -18.5 (*c* 0.8, $CHCl_3$); **IR** υ_{max} (thin film/cm^{-1}) 3276, 3138, 2926, 2852, 1723, 1283, 1150, 977, 835, 775; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.95 (1H, dt, *J* = 15.6, 6.5 Hz, H-3), 5.83 (1H, dt, *J* = 15.6, 1.5 Hz, H-2), 5.61-5.59 (2H, m, H-6, H-7), 4.92-4.88 (1H, m, H-10), 4.46 (2H, br s, NH_2), 4.18 (2H, q, *J* = 7.1 Hz, OCH_2CH_3), 4.11-4.08 (1H, m, H-8), 3.77 (1H, dd, *J* = 5.1, 2.4 Hz, H-9), 3.57 (2H, td, *J* = 6.6, 1.4 Hz, H-14), 2.31-2.25 (2H, m, H-4), 2.23-2.19 (2H, m, H-5), 1.60-1.55 (2H, m, H-11), 1.51-1.44 (2H, m, H-13), 1.28 (3H, t, *J* = 7.1 Hz, OCH_2CH_3), 1.28-1.22 (2H, m, H-12), 0.91 (9H, s, Si-C(CH_3)$_3$), 0.90 (9H, s, Si-C(CH_3)$_3$), 0.88 (9H, s, Si-C(CH_3)$_3$), 0.07 (3H, s, Si-CH_3), 0.05 (3H, s, Si-CH_3), 0.05 (3H, s, Si-CH_3), 0.03 (6H, s, Si-(CH_3)$_2$), 0.01 (3H, s, Si-CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.7, 156.5, 148.4, 131.0, 129.4, 121.9, 77.4, 76.1, 74.9, 63.3, 60.3, 33.1, 32.0, 30.9, 29.5, 26.13, 26.06, 26.04, 22.1, 18.36, 18.34, 14.4, -4.3, -4.35, -4.4, -4.5, -5.1; **HRMS** (ES^+) calcd. for $C_{35}H_{72}NO_7Si_3$ $[M+H]^+$ 702.4611, found 702.4614

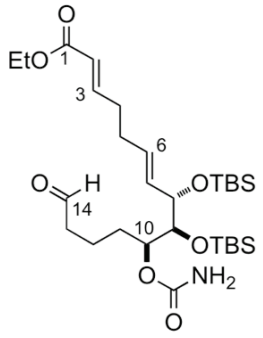
(2*E*,6*E*,8*S*,9*S*,10*S*)-Ethyl 8,9-bis((*tert*-butyldimethylsilyl)oxy)-10-(carbamoyloxy)-14-hydroxytetradeca-2,6-dienoate (170)



To a solution of tris-*tert*-butyldimethylsilyl ether **168** (130 mg, 0.185 mmol) in MeOH/CH_2Cl_2 (1:6, 5.0 mL) at 0 ºC was added (±)-CSA (4.3 mg, 18.5 μmol). After 1.5 h, saturated $NaHCO_3$ (5.0 mL) solution and CH_2Cl_2 (5.0 mL) were added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by flash column chromatography (10-20% EtOAC/Hexanes) provided alcohol **170** (100 mg, 93%) as a colourless oil.

R_f 0.26 (30% EtOAc/Hexanes); $[\alpha]_D^{20}$ -15.0 (*c* 0.2, $CHCl_3$); **IR υ_{max}** (thin film/cm^{-1}) 3466, 3364, 2979, 2929, 2854, 1714, 1366, 1312, 1278, 1188, 1128, 835, 775; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.95 (1H, dt, *J* = 15.7, 6.6 Hz, H-3), 5.83 (1H, dt, *J* = 15.7, 1.4 Hz, H-2), 5.60 (2H, m, *J* = 2.2 Hz, H-6, 7), 4.92-4.88 (1H, m, H-10), 4.53-4.42 (2H, br s, N$\underline{H}_2$), 4.18 (2H, q, *J* = 7.1 Hz, OC$\underline{H}_2$CH$_3$), 4.11-4.08 (1H, m, H-8), 3.78 (1H, dd, *J* = 5.2, 2.4 Hz, H-9), 3.61 (2H, t, *J* = 6.6 Hz, H-14), 2.31-2.27 (2H, m, H-4), 2.24-2.21 (2H, m, H-5), 1.61-1.52 (4H, m, H-11, H-13), 1.45-1.37 (2H, m, H-12), 1.28 (3H, t, *J* = 7.1 Hz, OCH$_2$C$\underline{H}_3$), 0.91 (9H, s, Si-C(C$\underline{H}_3$)$_3$), 0.90 (9H, s, Si-C(C$\underline{H}_3$)$_3$), 0.07 (3H, s, Si-C$\underline{H}_3$), 0.05 (6H, s, 2 × Si-C$\underline{H}_3$), 0.01 (3H, s, Si-C$\underline{H}_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.8, 156.5, 148.5, 130.9, 129.4, 121.9, 77.4, 75.8, 74.8, 63.0, 60.3, 32.8, 32.0, 30.8, 29.5, 26.05, 26.03, 21.9, 18.36, 18.33, 14.4, -4.33, -4.35, -4.4, -4.5; **HRMS** (ES^+) calcd. for $C_{29}H_{58}NO_7Si_2$ $[M+H]^+$ 588.3746, found 588.3743.

(2*E*,6*E*,8*S*,9*S*,10*S*)-Ethyl 8,9-bis((*tert*-butyldimethylsilyl)oxy)-10-(carbamoyloxy)-14-oxotetradeca-2,6-dienoate (169)

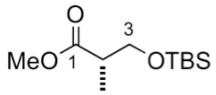


To a solution of alcohol **170** (40.0 mg, 68 μmol) in CH_2Cl_2 (5.0 mL) at 0 ºC was added $NaHCO_3$ (28.0 mg, 0.34 mmol) followed by Dess-Martin periodinane (86.0 mg, 0.20 mmol). The reaction mixture was stirred at 0 ºC for 1.5 h, and quenched by addition of cold hexane (5.0 mL) and cold toluene (5.0 mL). CH_2Cl_2 was then removed under reduced pressure and the resultant white suspension was filtered through Celite and washed with excess hexanes. The filtrate was concentrated under reduced pressure and purification by flash column chromatography (10-20% EtOAc/Hexanes) provided aldehyde **169** (31.0 mg, 80%) as a colourless oil.

***R*$_f$** 0.38 (30% EtOAc/Hexanes); $[\alpha]_D^{20}$ -22.2 (*c* 3.0, $CHCl_3$); **IR υ_{max}** (thin film/cm^{-1}) 3361, 2954, 2929, 2896, 2857, 1722, 1655, 1253, 1124, 836, 776; **^{1}H NMR** (400 MHz, C_6D_6) δ 9.32 (1H, t, *J* = 1.5 Hz, H-14), 7.01 (1H, dt, *J* = 15.6, 6.5 Hz, H-3), 5.90-5.86 (1H, m, H-2), 5.71 (1H, dd, *J* = 15.5, 5.5 Hz, H-7), 5.64-5.59 (1H, m, H-6), 5.17 (1H, dt, *J* = 9.5, 2.5 Hz, H-10), 4.25 (1H, td, *J* = 5.4, 0.9 Hz, H-8), 4.05 (2H, q, *J* = 7.1 Hz, OC$\underline{H}_2$CH$_3$), 4.01 (1H, dd, *J* = 5.3, 2.2 Hz, H-9), 2.02-1.96 (6H, m, H-4, H-5, H-13), 1.73-1.67 (3H, m, H-11, H-12a), 1.56-1.47 (1H, m, H-12b), 1.05 (9H, s, Si-C(C$\underline{H}_3$)$_3$), 1.03 (9H, s, Si-C(C$\underline{H}_3$)$_3$), 1.03-1.00 (3H, t, *J* = 7.1 Hz, OCH$_2$C$\underline{H}_3$), 0.19 (3H, s, Si-C$\underline{H}_3$), 0.16 (3H, s, Si-C$\underline{H}_3$), 0.13 (3H, s, Si-C$\underline{H}_3$), 0.12 (3H, s, Si-C$\underline{H}_3$); **^{13}C NMR** (100 MHz, C_6D_6) δ 200.7, 166.1, 156.7, 148.1, 131.0, 130.2, 122.5, 78.1, 75.4, 75.1, 60.1, 43.5, 31.9, 30.9, 29.2, 26.3, 26.2, 18.65, 18.60, 18.52, 14.4, -4.18, -4.25, -4.28, -4.31; **HRMS** (ES$^+$) calcd. for $C_{29}H_{56}NO_7Si_2$ $[M+H]^+$ 586.3590, found 586.3589.

7.5 Experimental procedures for Chapter 4

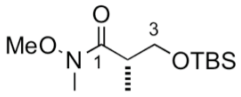
(*S*)-Methyl-3-((*tert*-butyldimethylsilyl)oxy)-2-methylpropanoate[73]



To a stirred solution of methyl (*S*)-3-hydroxy-2-methylpropionate **177** (17.1 g, 145 mmol) and imidazole (14.8 g, 217 mmol) in CH_2Cl_2 (300 mL) at 0 ºC was added TBSCl (26.2 g, 174 mmol) in portions. The reaction was stirred at rt for 12 h and quenched by addition of saturated $NaHCO_3$ (300 mL) solution. The aqueous phase was extracted with CH_2Cl_2 (4 × 200 mL) and the combined organic extracts were washed with brine (300 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by flash column chromatography (10% EtOAc/Hexanes) provided compound (32.0 g, 95%) as a colourless oil.

***R*$_f$** 0.52 (20% EtOAc/Hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.77 (1H, dd, *J* = 9.7, 6.9 Hz, H-3a), 3.68 (3H, s, OC$\underline{H}_3$), 3.65 (1H, dd, *J* = 10.0, 6.0 Hz, H-3b), 2.73-2.53 (1H, m, H-2), 1.13 (3H, d, *J* = 7.0 Hz, C$\underline{H}_3$), 0.87 (9H, s, Si-C(C$\underline{H}_3$)$_3$), 0.02 (6H, s, 2 × Si-C$\underline{H}_3$).

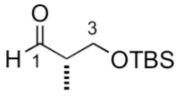
(*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-*N*-methoxy-*N*-2-dimethylpropanamide (179)[73]



To a stirred slurry of ester (32.0 g, 137 mmol) and Weinreb salt (20.0 g, 205 mmol) in THF (300 mL) was added *i*-PrMgCl (205 mL, 2 M soln. in THF, 415 mmol) dropwise, such that the internal temperature did not exceed -15 ºC. After 1 h at -10 ºC, saturated NH_4Cl (400 mL) solution was added and layers were separated. The aqueous phase was extracted with Et_2O (3 × 300 mL) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by flash column chromatography (5-20% Et_2O/Hexanes) afforded the Weinreb amide **179** (30.0 g, 84%) as a colourless oil.

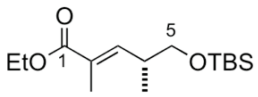
***R**f* 0.52 (20% EtOAc/Hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.83 (1H, dd, *J* = 9.5, 8.2 Hz, H-3a), 3.70 (3H, s, N-OC$\underline{H}_3$), 3.52 (1H, dd, *J* = 9.5, 6.1 Hz, H-3b), 3.19 (3H, s, N-C$\underline{H}_3$), 3.19-3.09 (1H, m, H-2), 1.06 (3H, d, *J* = 6.9 Hz, C$\underline{H}_3$), 0.86 (9H, s, Si-C(C$\underline{H}_3$)$_3$), 0.04 (3H, s, Si-C$\underline{H}_3$), 0.03 (3H, s, Si-C$\underline{H}_3$).

(*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-2-methylpropanal (176)[73]



To a stirred solution of Weinreb amide **179** (5.00 g, 19.1 mmol) in THF (50.0 mL) at -78 ºC was added DIBAL-H (38.3 mL, 1M soln. in Hexane, 38.3 mmol). After 1h at this temerature the mixture was cannulated into stirred solution of potassium sodium tartrate (250 mL) salt, further stirred vigorously for 1 h and extracted with Et_2O (3 × 150 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resultant pale yellow oil was used without purification in the next step.
***R**f* 0.62 (20% EtOAc/Hexanes); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.74 (1H, d, *J* = 1.6 Hz, H-1), 3.86 (1H, dd, *J* = 10.2, 5.2 Hz, H-3a), 3.80 (1H, dd, *J* = 10.2, 6.3 Hz, H-3b), 2.60-2.47 (1H, m, H-2), 1.09 (3H, d, *J* = 7.0 Hz, C$\underline{H}_3$), 0.87 (9H, s, Si-C(C$\underline{H}_3$)$_3$), 0.05 (6H, s, 2 × Si-C$\underline{H}_3$).

(*2E*,4*R*)-Ethyl 5-((*tert*-butyldimethylsilyl)oxy)-2,4-dimethylpent-2-enoate (181)[143]

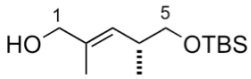


To a slurry of anyhydrous $Ba(OH)_2$ (4.76 g, 27.8 mmol) in THF (50.0 mL) was added triethylphosphonate (5.50 g, 23.1 mmol) and the resulting mixture stirred at rt for 45 min. A solution of aldehyde **176** (3.13 g, 15.4 mmol) in THF (50.0 mL) and H_2O (1.25 mL) was then added *via* cannula and the reaction mixture was stirred for a further 16 h. The reaction was then quenched with saturated NH_4Cl (100 mL) solution and layers were separated. The aqueous phase was extracted with Et_2O (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column

chromatography (10% EtOAc/Hexanes) afforded enoate **181** (3.27 g, 76%) as a colourless oil in 7:1 *E:Z* ratio.

***R**f* 0.48 (10% EtOAc/Hexanes); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.55 (1H, dq, *J* = 9.9, 1.4 Hz, H-3), 4.22-4.14 (2H, q, *J* = 7.1 Hz, $OC\underline{H}_2CH_3$), 3.51-3.43 (2H, m, H-5), 2.68 (1H, dq, *J* = 9.9, 6.6 Hz, H-4), 1.85 (3H, d, *J* = 1.4 Hz, C2-$C\underline{H}_3$), 1.28 (3H, t, *J* = 7.1 Hz, $OCH_2C\underline{H}_3$), 1.00 (3H, d, *J* = 6.7 Hz, C4-$C\underline{H}_3$), 0.87 (9H, s, Si-$C(C\underline{H}_3)_3$), 0.03 (3H, s, Si-$C\underline{H}_3$), 0.02 (3H, s, Si-$C\underline{H}_3$).

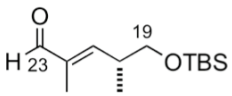
(*2E*,4*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-2,4-dimethylpent-2-en-1-ol (182)[143]



To a stirred solution of enoate **181** (2.80 g, 9.77 mmol) in THF (40.0 mL) at -78 ºC was added DIBAL-H (19.5 mL, 1M soln. in hexane, 19.5 mmol). After 1h at this temperature the mixture was cannulated into stirred solution of potassium sodium tartrate (150 mL) salt, further stirred vigorously for 1 h and extracted with Et_2O (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (10% EtOAc/Hexanes) afforded *E*-alcohol **182** (1.93 g, 81%) as a colourless oil.

***R**f* 0.28 (20% EtOAc/Hexanes); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.18 (1H, dq, *J* = 9.4, 1.3, H-3), 3.99 (2H, dd, *J* = 6.0, 0.9 Hz, H-1), 3.45 (1H, dd, *J* = 9.8, 6.1, H-5a), 3.36 (1H, dd, *J* = 9.8, 7.2 Hz, H-5b), 2.58 (1H, dq, *J* = 9.3, 6.7 Hz, H-4), 1.69 (3H, d, *J* = 1.4 Hz, C2-$C\underline{H}_3$), 0.95 (3H, d, *J* = 6.7 Hz, C4-$C\underline{H}_3$), 0.88 (9H, s, Si-$C(C\underline{H}_3)_3$), 0.03 (6H, s, 2 × Si-$C\underline{H}_3$).

(*2E*,4*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-2,4-dimethylpent-2-enal (175)

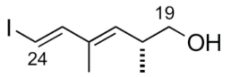


To a solution of alcohol **182** (500 mg, 2.04 mmol) in CH_2Cl_2 (20.0 mL) at 0 ºC was added $NaHCO_3$ (859 mg, 10.2 mmol) followed by Dess-Martin periodinane (2.60 g, 6.13 mmol). The reaction mixture was stirred at 0 ºC for 1.5 h, and quenched by addition of cold hexane (40.0 mL) and cold toluene (10.0 mL) and CH_2Cl_2 was then removed under reduced

pressure. The resultant white suspension was filtered through short pad of silica gel and Celite, eluting with 20% EtOAc/Hexanes. The filtrate was concentrated under reduced pressure to provide aldehyde **175** (440 mg, 90%) as a colourless oil which was immediately used without further purification.

***R*$_f$** 0.42 (10% EtOAc/Hexane); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.40 (1H, s, H-23), 6.32 (1H, dq, *J* = 9.7, 1.3 Hz, H-21), 3.59 (1H, dd, *J* = 9.9, 6.0 Hz, H-19a), 3.54 (1H, dd, *J* = 9.9, 6.5 Hz, H-19b), 2.89 (1H, ddd, *J* = 12.6, 9.7, 6.6 Hz, H-20), 1.77 (3H, d, *J* = 1.4 Hz, C22-C$\underline{H}_3$), 1.06 (3H, d, *J* = 6.8 Hz, C20-C$\underline{H}_3$), 0.87 (9H, s, Si-C(C$\underline{H}_3$)$_3$), 0.04 (3H, s, Si-C$\underline{H}_3$), 0.03 (3H, s, Si-C$\underline{H}_3$).

(2*R*,3*E*,5*E*)-6-Iodo-2,4-dimethylhexa-3,5-dien-1-ol (178)



To a solution of flame-dried $CrCl_2$ (1.12 g, 9.07 mmol) in THF (11.0 mL) at rt was added a solution of aldehyde **175** (220 mg, 0.907 mmol) and CHI_3 (1.07 g, 2.72 mmol) in 1,4-dioxane (65.0 mL). The reaction mixture was stirred for 2 h before it was quenched with saturated $NaHCO_3$ (50.0 mL) solution. The resulting mixture was diluted with EtOAc (200 mL), filtered through a short pad of Celite and washed with EtOAc (250 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 × 50 mL). The combine organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude material was directly subjected to TBAF deprotection.

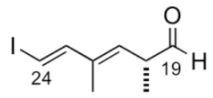
***R*$_f$** 0.8 (10% EtOAc/Hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.03 (1H, dd, *J* = 14.6, 0.8 Hz, H-23), 6.15 (1H, dd, *J* = 14.6, 0.6 Hz, H-24), 5.27 (1H, d, *J* = 9.5 Hz, H-21), 3.43 (2H, qd, *J* = 10.6, 6.5 Hz, H-19), 2.64 (1H, m, H-20), 1.74 (3H, d, *J* = 1.3 Hz, C22-C$\underline{H}_3$), 0.97 (3H, d, *J* = 6.7 Hz, C20-C$\underline{H}_3$), 0.88 (9H, s, Si-C(C$\underline{H}_3$)$_3$), 0.03 (3H, s, Si-C$\underline{H}_3$), 0.02 (3H, s, Si-C$\underline{H}_3$).

To a solution of crude **185** (332 mg, 0.907 mmol) in THF (10.0 mL) at 0 ºC was added TBAF (9.1 mL, 1 M in THF, 0.907 mmol). The reaction mixture was allowed to warm to rt and stirred for 12h. The reaction mixture was diluted with Et_2O (10.0 mL), poured onto water (20.0 mL) and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 20 mL) and the combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by flash

column chromatography (10% EtOAc/Hexanes) provided iodo-alcohol **178** (200 mg, 90%) as a pale yellow oil.

***R**f* 0.32 (10% EtOAc/Hexane); $[\alpha]_D^{20}$ +40.8 (*c* 0.7, $CHCl_3$); **IR** υ_{max} (thin film/cm^{-1}) 3374, 2959, 2926, 2870, 1726, 1707, 1451, 1178, 1035, 1018, 960, 752; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.06 (2H, dd, *J* = 14.7, 0.8 Hz, H-23), 6.22 (1H, dd, *J* = 14.7, 0.6 Hz, H-24), 5.27 (1H, dt, *J* = 9.6, 0.6 Hz, H-21), 3.55-3.49 (1H, m, H-19a), 3.44-3.39 (1H, m, H-19b), 2.78-2.67 (1H, m, H-20), 1.78 (3H, d, *J* = 1.3 Hz, C22-C<u>H</u>$_3$), 0.98 (3 H, d, *J* = 6.7 Hz, C20-C<u>H</u>$_3$); **^{13}C NMR** (100 MHz, C_6D_6) δ 149.6, 136.5, 136.0, 74.5, 67.6, 35.7, 16.8, 12.5; **HRMS** (ES^+) calcd. for $C_8H_{14}I_1O$ $[M+H]^+$ 253.0084, found 253.0079.

(2*R*,3*E*,5*E*)-6-Iodo-2,4-dimethylhexa-3,5-dienal (172)

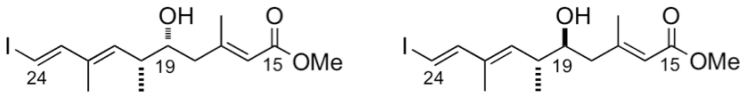


To a solution of alcohol **178** (300 mg, 1.19 mmol) in CH_2Cl_2 (40.0 mL) at 0 ºC was added $NaHCO_3$ (499 mg, 5.95 mmol) followed by Dess-Martin periodinane (1.51 g, 3.57 mmol). The reaction mixture was stirred at 0 ºC for 1.5 h and quenched by addition of cold hexane (50.0 mL) and cold toluene (10.0 mL). CH_2Cl_2 was then removed under reduced pressure and the resulting white suspension was filtered through Celite and short pad of silica gel (20% EtOAc/Hexanes) and concentrated under reduced pressure to provide aldehyde **172** (267 mg, 90%) as pale yellow oil. The resultant compound was immediately used without further purification.

***R**f* 0.46 (10% EtOAc/Hexanes); **^{1}H NMR** (400 MHz, C_6D_6) δ 9.05 (1H, d, *J* = 1.6, H-19), 6.81 (1H, dd, *J* = 14.7, 0.8 Hz, H-23), 5.91 (1H, dd, *J* = 14.7, 0.6 Hz, H-24), 4.73 (1H, ddt, *J* = 9.2, 1.3, 0.7 Hz, H-21), 2.69 (1H, ddd, *J* = 9.0, 7.1, 1.8 Hz, H-20), 1.19 (3H, d, *J* = 1.3 Hz, C22-C<u>H</u>$_3$), 0.79 (3H, d, *J* = 6.9 Hz, C20-C<u>H</u>$_3$).

(2*E*,5*R*,6*R*,7*E*,9*E*)-Methyl-5-hydroxy-10-iodo-3,6,8-trimethyldeca-2,7,9-trienoate (189)

(2*E*,5*S*,6*R*,7*E*,9*E*)-Methyl-5-hydroxy-10-iodo-3,6,8-trimethyldeca-2,7,9-trienoate



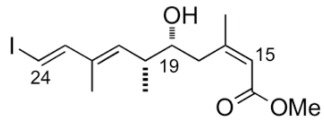
To a stirred solution of aldehyde **172** (200 mg, 0.799 mmol) and silyl ketene acetal **173** (253 mg, 1.36 mmol) containing CaH_2 (513 mg, 12.2 mmol) in CH_2Cl_2 (40.0 mL) at -95ºC was added BF_3•OEt_2 (5.0 mL, 0.5M soln. in CH_2Cl_2, 2.39 mmol) dropwise. After 20 min, the reaction mixture was allowed to warm to -80 ºC and a further aliquot of BF_3•OEt_2 (5.0 mL, 0.5M soln. in CH_2Cl_2, 2.39 mmol) was added. After 20 min the reaction mixture was quenched by the slow addition of saturated $NaHCO_3$ (50.0 mL) solution and allowed to warm to rt. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by flash column chromatography (1-10% EtOAc/Hexanes) provided a mixture of aldol products (210 mg, 70%) as colourless oils in 6:1 *syn*:*anti* ratio for *E* isomer and 3:1 *syn*:*anti* ratio for *Z* isomer.

189 *E-syn*: R_f 0.26 (10% EtOAc/Hexanes); $[\alpha]_D^{20}$ +17.7 (*c* 1.0, $CHCl_3$); **IR υ_{max}** (thin film/cm^{-1}) 3475, 2948, 1715, 1644, 1435, 1223, 1151, 1059, 950; **^{1}H NMR** (400 MHz, C_6D_6) δ 6.92 (1H, dd, *J* = 14.7, 0.8 Hz, H-23), 5.91 (1H, dd, *J* = 14.7, 0.5 Hz, H-24), 5.80 (1H, dd, *J* = 2.1, 1.2 Hz, H-16), 4.89 (1H, d, *J* = 10.0 Hz, H-21), 3.44 (3H, s, OC$\underline{H}_3$), 3.16-3.23 (1H, m, H-19), 2.21-2.11 (1H, m, H-20), 2.18 (H, d, *J* = 1.2 Hz, C17-C$\underline{H}_3$), 1.95 (1H, dd, *J* = 13.4, 2.3 Hz, H-18a), 1.75 (1H, dd, *J* = 13.7, 9.8 Hz, H-18b), 1.31 (3H, d, *J* = 1.2 Hz, C22-C$\underline{H}_3$), 0.87 (3H, d, *J* = 6.7 Hz, C20-C$\underline{H}_3$); **^{13}C NMR** (100 MHz, C_6D_6) δ 166.6, 157.2, 149.8, 136.5, 134.8, 118.1, 74.7, 73.1, 50.6, 46.7, 39.4, 19.0, 16.2, 12.1; **HRMS** (ES^+) calcd. for $C_{14}H_{25}I_1NO_3$ $[M+NH_4]^+$ 382.0874, found 382.0869.

***E-anti*: R_f** 0.27 (10% EtOAc/Hexanes); $[\alpha]_D^{20}$ +5.5 (*c* 0.2, $CHCl_3$); **IR υ_{max}** (thin film/cm^{-1}) 3496, 2948, 2926, 1711, 1646, 1436, 1227, 1152, 949, 839; **^{1}H NMR** (400 MHz, C_6D_6) δ 6.95 (1H, dd, *J* = 14.7, 0.8 Hz, H-23), 5.92 (1H, dd, *J* = 14.7, 0.6 Hz, H-24), 5.80 (1H, q, *J* = 1.2 Hz, H-16), 5.12 (1H, d, *J* = 10.0 Hz, H-21), 3.43 (3H, s, OC$\underline{H}_3$), 3.24 (1H, dq, *J* = 8.2, 4.2 Hz, H-19), 2.20 (3H, d, *J* = 1.3 Hz, C17-C$\underline{H}_3$), 2.17-2.14 (1H, m, H-20), 1.85 (1H,

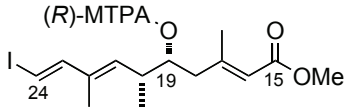
dd, *J* = 4.1, 0.9 Hz, H-18a), 1.85-1.84 (1H, m, H-18b), 1.32 (3H, d, *J* = 1.3 Hz, C22-C$\underline{H}_3$), 0.77 (3H, d, *J* = 6.7 Hz, C20-C$\underline{H}_3$); **^{13}C NMR** (100 MHz, C_6D_6) δ 166.7, 157.0, 149.8, 135.6, 135.2, 118.1, 74.7, 72.8, 50.6, 46.4, 38.7, 19.1, 17.1, 12.1; **HRMS** (ES^+) calcd. for $C_{14}H_{25}I_1NO_3$ $[M+NH_4]^+$ 382.0874, found 382.0871.

(2*Z*,5*R*,6*R*,7*E*,9*E*)-Methyl 5-hydroxy-10-iodo-3,6,8-trimethyldeca-2,7,9-trienoate



***(Z)-syn*: R_f** 0.29 (10% EtOAc/Hexanes); $[\alpha]_D^{20}$ +20.7 (*c* 1.7, $CHCl_3$); **IR υ_{max}** (thin film/cm^{-1}) 3450, 3442, 2970, 2926, 1714, 1651, 1447, 1280, 1180, 1015, 949, 867; **^{1}H NMR** (500 MHz, C_6D_6) δ 6.98 (1H, d, *J* = 14.7 Hz, H-23), 5.90 (1H, d, *J* = 14.6 Hz, H-24), 5.77 (1H, d, *J* = 1.2 Hz, H-16), 5.14 (1H, d, *J* = 10.0 Hz, H-21), 3.47 (1H, dtd, *J* = 10.4, 7.1, 2.9 Hz, H-19), 3.28 (3H, s, OC$\underline{H}_3$), 3.19 (1H, d, *J* = 7.4 Hz, O$\underline{H}$), 2.98 (1H, dd, *J* = 12.6, 10.6 Hz, H-18a), 2.44 (1H, dt, *J* = 10.0, 6.7 Hz, H-20), 2.15 (1H, dd, *J* = 12.6, 2.5 Hz, H-18b), 1.54 (3H, d, *J* = 1.3 Hz, C17-C$\underline{H}_3$), 1.39 (3H, d, *J* = 1.1 Hz, C22-C$\underline{H}_3$), 1.09 (3H, d, *J* = 6.7 Hz, C20-C$\underline{H}_3$); **^{13}C NMR** (125 MHz, C_6D_6) δ 168.5, 158.7, 150.0, 137.3, 134.7, 118.1, 74.8, 74.3, 51.0, 41.1, 39.7, 25.5, 16.6, 12.2; **HRMS** (ES^+) calcd. for $C_{14}H_{22}I_1O_3$ $[M+H]^+$ 365.0608, found 365.0612.

(*R*)-Mosher ester of 189 (192)

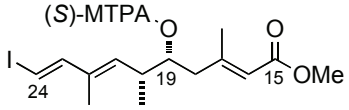


To a stirred mixture of alcohol **189** (20.0 mg, 54.9 μmol), DCC (45.0 mg, 219 μmol) and DMAP (13.0 mg, 109 μmol) in CH_2Cl_2 (2.0 mL) at rt was added (+)-(*R*)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (26.0 mg, 109 μmol) in one portion. After 12 h, the crude reaction mixture was directly purified by flash column chromatography (5% EtOAc/Hexanes) to give (*R*)-MTPA ester **192** (30.0 mg, 94%).

R_f 0.46 (10% EtOAc/Hexanes); **^{1}H NMR** (400 MHz; $CDCl_3$) δ 7.48 (2H, d, *J* = 8.3 Hz, Ph-$\underline{H}$), 7.43-7.37 (3H, m, Ph-$\underline{H}$), 7.01 (1H, dd, *J* = 14.7, 0.8 Hz, H-23), 6.28 (1H, dd, *J* =

14.7, 0.5 Hz, H-24), 5.61 (1H, d, *J* = 1.2 Hz, H-16), 5.26 (1H, dd, *J* = 9.9, 0.6 Hz, H-21), 5.23 (1H, dt, *J* = 7.7, 5.8 Hz, H-19), 3.66 (3H, s, OC$\underline{H}_3$), 3.46 (3H, d, *J* = 1.0 Hz, MTPA-OC$\underline{H}_3$), 2.82 (1H, dq, *J* = 9.8, 6.6 Hz, H-20), 2.42 (1H, s, H-18a), 2.41 (1H, dd, *J* = 2.5, 0.8 Hz, H-18b), 2.17 (3H, d, *J* = 1.3 Hz, C17-C$\underline{H}_3$), 1.74 (3H, d, *J* = 1.3 Hz, C22-C$\underline{H}_3$), 1.03 (3H, d, *J* = 6.8 Hz, C20-C$\underline{H}_3$).

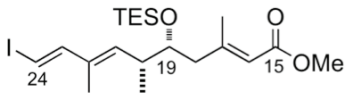
(*S*)-Mosher ester of 189 (193)



To a stirred mixture of alcohol **189** (20.0 mg, 54.9 μmol), DCC (45.0 mg, 219 μmol) and DMAP (13.0 mg, 109 μmol) in CH_2Cl_2 (2.0 mL) at rt was added (+)-(*S*)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (26.0 mg, 109 μmol) in one portion. After 12 h, the crude reaction mixture was purified directly by flash column chromatography (5% EtOAc/Hexanes) to give (*S*)-MTPA ester **193** (25.0 mg, 78%).

***R**_f* 0.46 (10% EtOAc/Hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49-7.47 (2H, m, Ph-$\underline{H}$), 7.37-7.41 (3H, m, Ph-$\underline{H}$), 6.92 (1H, dd, *J* = 14.7, 0.7 Hz, H-23), 6.23 (1H, dd, *J* = 14.7, 0.5 Hz, H-24), 5.68 (1H, q, *J* = 1.1 Hz, H-16), 5.23 (1H, dt, *J* = 7.2, 6.1 Hz, H-19), 5.14 (1H, d, *J* = 10.4 Hz, H-21), 3.68 (3H, s, OC$\underline{H}_3$), 3.51 (3H, d, *J* = 1.2 Hz, MTPA-OC$\underline{H}_3$), 2.73 (1H, dq, *J* = 9.9, 6.6 Hz, H-20), 2.45 (1H, d, *J* = 0.8 Hz, H-18a), 2.43 (1H, m, H-18b), 2.19 (3H, d, *J* = 1.3 Hz, C17-C$\underline{H}_3$), 1.67 (3H, d, *J* = 1.3 Hz, C22-C$\underline{H}_3$), 0.94 (3H, d, *J* = 6.8 Hz, C20-C$\underline{H}_3$).

(2*E*,5*R*,6*R*,7*E*,9*E*)-Methyl-10-iodo-3,6,8-trimethyl-5-((triethylsilyl)oxy)deca-2,7,9-trienoate (194)

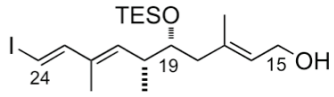


To a solution of alcohol **189** (250 mg, 0.686 mmol) in CH_2Cl_2 (7.0 mL) at -78 ºC was added 2,6-lutidine (240 μL, 2.06 mmol) and TESOTf (250 μL, 1.10 mmol). After 4 h, saturated NH_4Cl (15.0 mL) solution and CH_2Cl_2 (15.0 mL) were added and the layers were

separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by flash column chromatography (5% EtOAc/Hexanes) provided TES ether **194** (230 mg, 96%) as a colourless oil.

***R*$_f$** 0.73 (10% EtOAc/Hexanes); $[\alpha]_D^{20}$ +33.6 (*c* 0.5, $CHCl_3$); **IR υ_{max}** (thin film/cm^{-1}) 2953, 2911, 2876, 1720, 1647, 1435, 1223, 1150, 1087, 1008, 739, 725; **^{1}H NMR** (300 MHz, C_6D_6) δ 7.02 (1H, dd, *J* = 14.6, 0.7 Hz, H-23), 5.93 (1H, d, *J* = 14.6 Hz, H-24), 5.87 (1H, q, *J* = 1.1 Hz, H-16), 5.12 (1H, dd, *J* = 9.7, 0.4 Hz, H-21), 3.64 (1H, dt, *J* = 6.6, 5.4 Hz, H-19), 3.44 (3H, s, OC$\underline{H}_3$), 2.46-2.39 (1H, m, H-20), 2.25 (3H, d, *J* = 1.3 Hz, C17-C$\underline{H}_3$), 2.08-2.10 (1H, td, *J* = 6.10, 0.95 Hz, H-18a), 2.07 (1 H, d, *J* = 0.8 Hz, H-18b), 1.36 (3H, d, *J* = 1.2 Hz, C22-C$\underline{H}_3$), 0.96 (6H, m, 3 × Si-C$\underline{H}_2$CH$_3$), 0.89 (3H, d, *J* = 6.8 Hz, C20-C$\underline{H}_3$), 0.56 (9H, m, 3 × Si-CH$_2$C$\underline{H}_3$); **^{13}C NMR** (75 MHz, C_6D_6) δ 166.6, 156.5, 149.9, 137.2, 134.4, 118.7, 74.7, 74.5, 50.6, 46.9, 38.5, 19.5, 15.6, 12.1, 7.2, 5.6; **HRMS** (ES$^+$) calcd. for $C_{20}H_{40}INO_3Si$ $[M+NH_4]^+$ 496.1738, found 496.1734.

(2*E*,5*R*,6*R*,7*E*,9*E*)-10-Iodo-3,6,8-trimethyl-5-((triethylsilyl)oxy)deca-2,7,9-trien-1-ol (195)

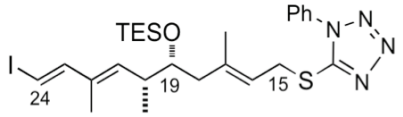


To a stirred solution of enoate **194** (330 mg, 0.689 mmol) in THF (40.0 mL) at -78 ºC was added DIBAL-H (1.4 mL, 1M soln. in hexane, 1.38 mmol). After 1h at this temerature the mixture was added *via* cannula into a stirred solution of potassium sodium tartrate (50.0 mL) salt, further stirred vigorously for 1 h and extracted with Et_2O (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash column chromatography (10% EtOAc/Hexanes) afforded alcohol **195** (250 mg, 81%) as a colourless oil.

***R*$_f$** 0.29 (20% EtOAc/Hexanes); $[\alpha]_D^{20}$ +18.5 (*c* 0.7, $CHCl_3$); **IR υ_{max}** (thin film/cm^{-1}) 3342, 2955, 2911, 1457, 1003, 948, 744, 725; **^{1}H NMR** (400 MHz, C_6D_6) δ 7.07 (1H, dd, *J* = 14.6, 0.8 Hz, H-23), 5.93 (1H, dd, *J* = 14.6, 0.6 Hz, H-24), 5.38 (1H, ddd, *J* = 7.8, 5.4, 1.2 Hz, H-16), 5.27 (1H, d, *J* = 9.8 Hz, H-21), 3.94 (2H, d, *J* = 6.8 Hz, H-15), 3.67 (1H, td, *J* = 6.2, 4.7 Hz, H-19), 2.50 (1H, ddd, *J* = 9.8, 6.8, 4.7, H-20), 2.14 (2H, qd, *J* = 13.6, 6.2 Hz,

H-18), 1.51 (3H, t, *J* = 0.6 Hz, C17-C<u>H</u>$_3$), 1.41 (3H, d, *J* = 1.3 Hz, C22-C<u>H</u>$_3$), 0.97-1.01 (6H, m, 3 × Si-C<u>H</u>$_2$CH$_3$)$_3$, C20-C<u>H</u>$_3$), 0.58 (9H, m, 3 × Si-CH$_2$C<u>H</u>$_3$); **^{13}C NMR** (100 MHz, C_6D_6) δ 150.0, 138.3, 135.0, 133.9, 129.0, 74.7, 74.2, 59.3, 45.9, 37.8, 16.9, 15.1, 12.1, 7.3, 5.6; **HRMS** (ES$^+$) calcd. for $C_{19}H_{40}INO_2Si$ $[M+NH_4]^+$ 468.1789, found 468.1787.

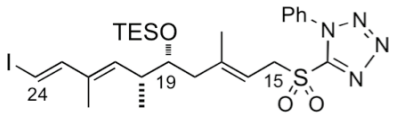
5-(((2*E*,5*R*,6*R*,7*E*,9*E*)-10-Iodo-3,6,8-trimethyl-5-((triethylsilyl)oxy)deca-2,7,9-trien-1-yl)thio)-1-phenyl-1H-tetrazole (196)



To a stirred solution of alcohol **195** (130 mg, 0.288 mmol), in THF (30.0 mL) at 0 ºC was added 1*H*-mercaptophenyltetrazole (66.0 mg, 0.378 mmol), PPh_3 (99.0 mg, 0.378 mmol) followed by DIAD (74.0 µL, 0.378 mmol) dropwise. The reaction mixture was allowed to warm to rt for 1.5 h, before a saturated NH_4Cl (20.0 mL) solution and Et_2O (30.0 mL) were added. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by flash column chromatography (10% EtOAc/Hexanes) gave sulfide **196** (140 mg, 80 %) as a colourless oil.

***R*$_f$** 0.62 (10% EtOAc/Hexanes) $[\alpha]_D^{20}$ +58.5 (*c* 1.0, $CHCl_3$); **IR υ_{max}** (thin film/cm^{-1}) 3068, 2955, 2911, 2875, 1597, 1500, 1384, 1234, 1092, 1015, 950, 759, 742, 725; **^{1}H NMR** (400 MHz, C_6D_6) δ 7.17-7.19 (2H, m, Ar-<u>H</u>), 7.05 (1H, dd, *J* = 14.6, 0.7 Hz, H-23), 6.87-6.93 (3H, m, Ar-<u>H</u>), 5.95 (1H, dd, *J* = 14.6, 0.5 Hz, H-24), 5.37 (1H, td, *J* = 7.9, 1.1 Hz, H-16), 5.22 (1H, dt, *J* = 9.8, 0.5 Hz, H-21), 3.90 (2H, qd, *J* = 14.6, 7.9 Hz, H-15), 3.62 (1H, td, *J* = 6.2, 4.7 Hz, H-19), 2.42 (1H, ddd, *J* = 9.7, 6.8, 4.6 Hz, H-20), 2.07 (2H, ddt, *J* = 20.2, 13.9, 6.6 Hz, H-18), 1.58 (3H, d, *J* = 1.3 Hz, C17-C<u>H</u>$_3$), 1.40 (3H, d, *J* = 1.2 Hz, C22-C<u>H</u>$_3$), 0.96 (6H, s, 3 × Si-C<u>H</u>$_2$CH$_3$), 0.92 (3H, d, *J* = 6.8 Hz, C20-C<u>H</u>$_3$), 0.53-0.58 (9H, m, 3 × Si-CH$_2$C<u>H</u>$_3$); **^{13}C NMR** (100 MHz, C_6D_6) δ 154.1, 150.0, 139.8, 138.0, 134.3, 134.0, 129.64, 129.61, 123.9, 120.8, 74.5, 74.3, 45.8, 37.7, 31.6, 16.9, 15.0, 12.1, 7.3, 5.6; **HRMS** (ASAP) calcd. for $C_{26}H_{40}IN_4OSSi$ $[M+H]^+$ 611.1731, found 611.1729.

5-(((2*E*,5*R*,6*R*,7*E*,9*E*)-10-Iodo-3,6,8-trimethyl-5-((triethylsilyl)oxy)deca-2,7,9-trien-1-yl)sulfonyl)-1-phenyl-1H-tetrazole (171)

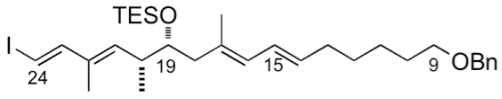


A mixture of ammonium molybdate (1.6 mg, 1.31 μmol), hydrogen peroxide (0.15 mL, 1.31 mmol, 30% v/v) and HMPA (0.15 mL) was stirred at 0 ºC for 15 min. The resulting bright yellow solution was added dropwise to a solution of sulfide **196** (80.0 mg, 0.131 mmol) in MeOH (2.0 mL) at 0 ºC. After 21 h, the reaction mixture was diluted with MeOH (2.0 mL), and H_2O (10.0 mL) was added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by flash column chromatography (5% Acetone/Hexanes) provided sulfone **171** (79.0 mg, 95%) as a colourless oil.

***R*$_f$** 0.43 (20% Acetone/Hexanes); $[\alpha]_D^{20}$ +33.6 (*c* 0.5, $CHCl_3$); **IR υ_{max}** (thin film/cm^{-1}) 3069, 2955, 2925, 2875, 1498, 1461, 1343, 1156, 1107, 1015, 950, 761, 739; **^{1}H NMR** (400 MHz, C_6D_6) δ 7.26-7.33 (2H, m, Ar-H), 7.05 (1H, dd, *J* = 14.6, 0.8 Hz, H-23), 6.85-6.86 (3H, m, Ar-H), 5.94 (2H, dd, *J* = 14.6, 0.5 Hz, H-24), 5.29 (1H, td, *J* = 7.9, 0.9 Hz, H-16), 5.22 (1H, d, *J* = 9.3 Hz, H-21), 4.08 (2H, dd, *J* = 7.9, 3.0 Hz, H-15), 3.62 (1H, td, *J* = 6.5, 4.1 Hz, H-19), 2.38-2.35 (1H, m, H-20), 2.10 (1H, dd, *J* = 13.6, 6.9 Hz, H-18a), 2.01 (1H, dd, *J* = 13.6, 6.1 Hz, H-18b), 1.50 (3H, d, *J* = 1.2 Hz, C17-CH$_3$), 1.39 (3H, d, *J* = 1.2 Hz, C22-CH$_3$), 0.88-1.01 (6H, m, 3 × Si-CH$_2$CH$_3$), 0.86 (3H, d, *J* = 6.7 Hz, C20-CH$_3$), 0.46-0.60 (9H, m, 3 × Si-CH$_2$CH$_3$); **^{13}C NMR** (100 MHz, C_6D_6) δ 154.0, 149.8, 146.8, 136.6, 134.8, 133.5, 131.0, 129.4, 125.4, 111.0, 74.6, 72.6, 56.2, 45.9, 39.2, 17.0, 16.3, 12.1, 7.2, 6.9; **HRMS** (ES$^+$) calcd. for $C_{26}H_{40}IN_5O_3SSi$ $[M+NH_4]^+$ 660.1895, found 660.1893.

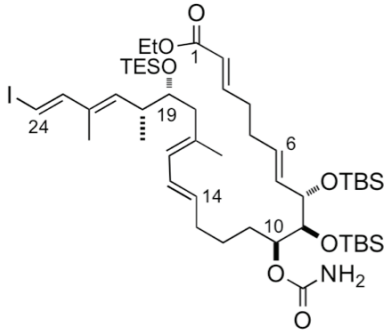
7.6 Experimental procedures for Chapter 5

(((1*E*,3*E*,5*R*,6*R*,8*E*,10*E*)-16-(Benzyloxy)-1-iodo-3,5,8-trimethylhexadeca-1,3,8,10-tetraen-6-yl)oxy)triethylsilane (209)



To a solution of sulfone **171** (10.0 mg, 15.7 μmol) in THF (1.0 mL) at -78 ºC was added NaHMDS (12 μL, 2M soln. in THF, 12.5 μmol). After 5 min, a solution of aldehyde **208** (3.0 mg, 10.5 μmol) in THF (0.5 mL) was added dropwise and the reaction mixture was allowed to warm to -60 ºC. After 1 h, MeOH (0.5 mL) was added followed by saturated NH_4Cl (5.0 mL) solution and the reaction mixture was warmed to rt. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 5 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by flash column chromatography (5% EtOAc/Hexanes) provided alkene **209** (5.0 mg, 80%) as a colourless oil, in 2:1 *E*:*Z* ratio.
***R**f* 0.65 (10% EtOAc/Hexanes); **IR υ_{max}** (thin film/cm^{-1}) 3367, 3184, 2919, 1675, 1277, 1181, 1106, 676, 611; **^{1}H NMR** (400 MHz, C_6D_6) δ 7.32 (2H, d, *J* = 6.9 Hz, Ar-H), 7.20 (3H, m, Ar-H), 7.08 (1H, dd, *J* = 14.6, 0.8 Hz, H-23), 6.35 (1H, ddt, *J* = 14.9, 10.7, 1.4 Hz, H-15), 5.97 (1H, d, *J* = 11.0 Hz, H-16), 5.93 (1H, dd, *J* = 14.6, 0.6 Hz, H-24), 5.61 (1H, dt, *J* = 14.8, 7.2 Hz, H-14), 5.29 (1H, d, *J* = 10.4 Hz, H-21), 4.35 (2H, s, CH_aH_bAr), 3.73 (1H, td, *J* = 6.2, 4.8 Hz, H-19), 3.34-3.28 (2H, m, H-9), 2.57-2.50 (1H, m, H-20), 2.29-2.17 (2H, m, H-18), 2.09-2.04 (2H, m, H-13), 1.72 (3H, d, *J* = 0.9 Hz, C17-CH_3), 1.61-1.55 (2H, m, H-10), 1.42 (3H, d, *J* = 1.3 Hz, C22-CH_3), 1.33-1.40 (4H, m, H-11, H-12), 0.97-1.05 (9H, m, 3 × Si-$CH_2CH_3)_3$, C20-CH_3), 0.57-0.65 (9H, m, 3 × Si-CH_2CH_3); **^{13}C NMR** (100 MHz, C_6D_6) δ 150.1, 138.4, 133.9, 133.4, 132.4, 128.7, 128.6, 127.7, 127.6, 127.1, 125.0, 75.0, 74.0, 73.0, 70.5, 46.4, 38.0, 33.4, 30.2, 29.9, 26.3, 17.3, 15.3, 12.1, 7.4, 5.6; **HRMS** (ES^+) calcd. for $C_{32}H_{55}INO_2Si$ $[M+NH_4]^+$ 640.3041, found 640.3038.

(2*E*,6*E*,8*S*,9*S*,10*S*,14*E*,16*E*,19*R*,20*R*,21*E*,23*E*)-Ethyl 8,9-bis((*tert*-butyldimethylsilyl)-oxy)-10-(carbamoyloxy)-24-iodo-17,20,22-trimethyl-19-((triethylsilyl)oxy)tetracosa-2,6,14,16,21,23-hexaenoate (210)

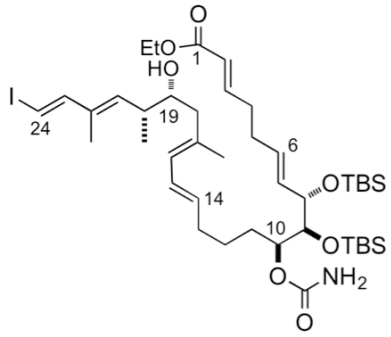


To a solution of sulfone **171** (57.0 mg, 89 μmol) in THF (3.0 mL) at -78 ºC was added NaHMDS (36.0 μL, 2 M in THF, 71.7 μmol). After 5 min, a solution of aldehyde **169** (35.0 mg, 59.7 μmol) in THF (2.0 mL) was added dropwise and the reaction mixture was allowed to warm to -50 ºC. After 1 h, MeOH (1.0 mL) was added followed by saturated NH_4Cl (30.0 mL) solution and the reaction mixture was warmed to rt. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by flash column chromatography (5% EtOAc/Hexanes) provided alkene **210** (46.0 mg, 78%) as a colourless oil in 7:1 *E*:*Z* ratio.

R_f 0.65 (10% EtOAc/Hexanes); $[\alpha]_D^{20}$ +35.0 (*c* 3.5, $CHCl_3$); **IR υ_{max}** (thin film/cm^{-1}) 2953, 2911, 2876, 1720, 1647, 1435, 1223, 1150, 1087, 1008, 739, 725; **^{1}H NMR** (400 MHz, C_6D_6) δ 7.08 (1H, dd, *J* = 14.6, 0.7 Hz, H-23), 7.00 (1H, dt, *J* = 15.6, 6.5 Hz, H-3), 6.37 (1H, dd, *J* = 15.0, 10.8 Hz, H-15), 5.99-5.95 (1H, m, H-14), 5.95 (1H, dd, *J* = 14.6, 0.5 Hz, H-24), 5.89-5.84 (1H, m, H-2), 5.75 (1H, dd, *J* = 15.6, 5.8 Hz, H-7), 5.67-5.57 (2H, m, H-6, H-16), 5.32 (1H, d, *J* = 9.7 Hz, H-21), 5.27-5.23 (1H, m, H-10), 4.28 (1H, t, *J* = 5.3 Hz, H-8), 4.07 (2H, q, *J* = 7.1 Hz, $OC\underline{H}_2CH_3$), 4.03 (1H, dd, *J* = 5.0, 2.1 Hz, H-9), 3.74 (1H, td, *J* = 6.2, 4.6 Hz, H-19), 2.55 (1H, m, H-20), 2.22 (2H, m, H-18), 2.00-1.94 (4H, m, H-4, H-5), 1.91-1.80 (2H, m, H-11), 1.72 (3H, d, *J* = 0.8 Hz, C17-$C\underline{H}_3$), 1.76-1.65 (2H, m, H-13), 1.60-1.51 (2H, m, H-12), 1.44 (3H, d, *J* = 1.2 Hz, C22-$C\underline{H}_3$), 1.06 (9H, s, Si-$C(C\underline{H}_3)_3$), 1.05 (9H, s, Si-$C(C\underline{H}_3)_3$), 1.06-0.98 (12H, m, C20-$C\underline{H}_3$, $OCH_2\underline{CH}_3$, $\underline{Si}$-$(C\underline{H}_2CH_3)_3$), 0.64-0.57 (9H, m, Si-$(CH_2C\underline{H}_3)_3$), 0.20 (3H, s, Si-$C\underline{H}_3$), 0.19 (3H, s, Si-$C\underline{H}_3$), 0.14 (3H, s, Si-$C\underline{H}_3$), 0.13 (3H, s, Si-$C\underline{H}_3$); **^{13}C NMR** (100 MHz, C_6D_6) δ 166.0, 156.6, 150.1, 148.0,

138.5, 133.8, 133.2, 132.5, 131.3, 130.0, 128.7, 127.3, 122.4, 78.2, 75.58, 75.56, 74.9, 74.0, 60.0, 46.4, 37.8, 33.4, 32.0, 31.0, 29.8, 26.4, 26.32, 26.26, 18.62, 18.56, 17.3, 15.1, 14.4, 12.1, 7.4, 5.6, -4.1, -4.18, -4.22, -4.3; **HRMS** (ES^+) calcd. for $C_{48}H_{92}IN_2O_7Si_3$ $[M+NH_4]^+$ 1019.5252, found 1019.5258.

(2*E*,6*E*,8*S*,9*S*,10*S*,14*E*,16*E*,19*R*,20*R*,21*E*,23*E*)-Ethyl 8,9-bis((*tert*-butyldimethylsilyl)-oxy)-10-(carbamoyloxy)-19-hydroxy-24-iodo-17,20,22-trimethyltetracosa-2,6,14,16,21,23-hexaenoate (211)

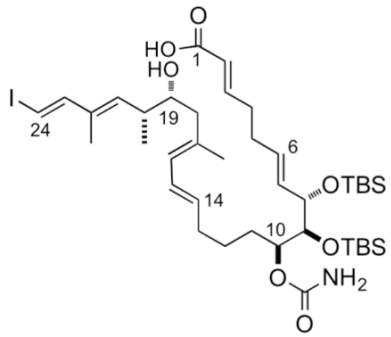


To a solution of **210** (5.0 mg, 0.499 μmol) in THF (2.0 mL) at 0 ºC was added a buffered solution of pyridine hydrofluoride (0.2 mL, stock solution prepared from 0.5 mL of pyridine hydrofluoride, 1.0 mL of pyridine, and 4.0 mL of THF) dropwise. After stirring for 1h, the reaction was quenched by the addition of saturated $NaHCO_3$ (5.0 mL) solution, diluted with Et_2O (15.0 mL) and brine (10.0 mL), and finally extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by flash column chromatography (10% EtOAc/Hexanes) gave alcohol **211** (3.9 mg, 88%) as a colourless oil.

R_f 0.30 (20% EtOAc/Hexane); $[\alpha]_D^{20}$ +30.6 (*c* 1.0, $CHCl_3$); **IR υ_{max}** (thin film/cm^{-1}) 3509, 3370, 2955, 2975, 2857, 1723, 1655, 1472, 1463, 1255, 1126, 837, 776; **^{1}H NMR** (400 MHz, C_6D_6) δ 7.04 (1H, dt, *J* = 15.7, 6.4 Hz, H-3), 6.97 (1H, dd, *J* = 14.6, 0.7 Hz, H-23), 6.34 (1H, dd, *J* = 15.0, 10.8 Hz, H-15), 5.95-5.86 (2H, m, H-2, H-16) 5.91 (1H, dd, *J* = 14.6, 0.5 Hz, H-24), 5.76 (1H, dd, *J* = 15.5, 5.6 Hz, H-7), 5.66-5.59 (2H, m, H-6, H-14), 5.28 (1H, ddd, *J* = 9.3, 3.2, 2.3 Hz, H-10), 5.10 (1H, d, *J* = 9.9 Hz, H-21), 4.29 (1H, t, *J* = 4.9 Hz, H-8), 4.09-4.02 (1H, m, H-9) 4.06 (2H, *J* = 7.1 Hz, O<u>H</u>$_2$CH$_3$), 3.69 (2H, br s, N<u>H</u>$_2$), 3.38 (1H, ddd, *J* = 9.7, 7.0, 2.7 Hz, H-19), 2.41 (1H, dt, *J* = 10.0, 6.7 Hz, H-20), 2.22-2.17 (2H, m, H-13), 2.14 (1H, dd, *J* = 13.8, 2.4 Hz, H-18a), 2.04-1.94 (4H, m, H-4,

H-5), 1.91 (1H, dd, *J* = 13.9, 10.0 Hz, H-18b), 1.89-1.82 (2H, m, H-11), 1.70-1.57 (5 H, m, H-12), 1.62 (3H, s, C17-C$\underline{H}_3$), 1.40 (3H, d, *J* = 1.2 Hz, C22-C$\underline{H}_3$), 1.08-1.05 (3H, m_{obs}, C20-C$\underline{H}_3$), 1.07 (9H, s, Si-C(CH_3)$_3$), 1.06 (9H, s, Si-C(C$\underline{H}_3$)$_3$), 1.03 (3H, t, *J* = 7.1 Hz, OCH$_2$C$\underline{H}_3$), 0.21 (3H, s, Si-C$\underline{H}_3$), 0.19 (3H, s, Si-C$\underline{H}_3$), 0.15 (3H, s, Si-C$\underline{H}_3$), 0.14 (3H, s, Si-C$\underline{H}_3$); **^{13}C NMR** (100 MHz, C_6D_6) δ 166.1, 156.3, 150.1, 148.2, 137.4, 134.5, 133.6, 132.9, 131.3, 130.0, 128.7, 127.2, 122.4, 78.2, 75.5, 75.4, 74.2, 72.8, 60.1, 46.3, 39.3, 33.3, 32.0, 31.0, 29.6, 26.3, 26.2, 26.13, 18.62, 18.55, 16.7, 16.51, 14.4, 12.1, -4.15, -4.19, -4.23, -4.26; **HRMS** (ES$^+$) calcd. for $C_{42}H_{78}IN_2O_7Si_2$ $[M+NH_4]^+$ 905.4387, found 905.4394.

(2*E*,6*E*,8*S*,9*S*,10*S*,14*E*,16*E*,19*R*,20*R*,21*E*,23*E*)-8,9-Bis((*tert*-butyldimethylsilyl)oxy)-10-(carbamoyloxy)-19-hydroxy-24-iodo-17,20,22-trimethyltetracosa-2,6,14,16,21,23-hexaenoic acid (212)

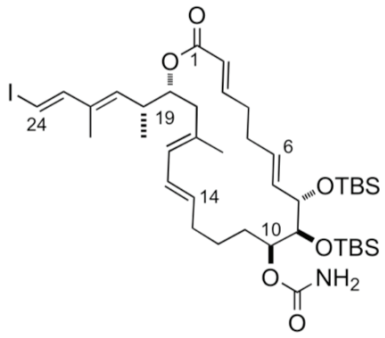


To a solution of ethyl ester **211** (14.0 mg, 15.7 µmol) in Et_2O (1.0 ml) was added potassium trimethylsilanolate (6.1 mg, 47.3 µmol) in one portion. The slightly yellowish solution was stirred at rt for 24 h and then quenched by addition of $NaHSO_4$ (100 µL, 0.1 M), buffered with Na_2SO_4, filtered and concentrated under reduced pressure. The resulting crude residue was dried under high vacuum and immediately used in the next step.

***R**$_f$* 0.23 (30% EtOAc/Hexane and drop of AcOH); **^{1}H NMR** (400 MHz, C_6D_6) δ 7.14-7.08 (1H, m, H-3), 7.00 (1 H, dd, *J* = 14.6, 0.8 Hz, H-23), 6.42-6.32 (1H, m, H-15), 6.15 (1H, d, *J* = 15.5 Hz, H-2), 6.00 (1H, d, *J* = 10.8 Hz, H-16), 5.92 (1H, d, *J* = 14.6 Hz, H-24), 5.81-5.74 (1H, m, H-7), 5.71-5.67 (1H, m, H-6), 5.61 (1H, dd, *J* = 14.7, 7.4 Hz, H-14), 5.30-5.27 (1H, m, H-10), 5.20 (1H, d, *J* = 10.6 Hz, H-21), 4.31-4.26 (1H, m, H-8), 4.06 (1H, dd, *J* = 5.3, 2.2 Hz, H-9), 3.53-3.46 (1H, m, H-19), 2.52-2.43 (1H, m, H-20), 2.24-2.14 (3H, m, H-13, H-18a), 2.15-2.08 (2H, m, H-4), 2.08-2.00 (3H, m, H-5, H-18b), 1.91-1.82 (2H, m, H-11), 1.69 (3H, s, C17-C$\underline{H}_3$), 1.68-1.66 (2H, m, H-12), 1.43 (3H, d, *J* = 1.2 Hz, C22-

C$\underline{H}_3$), 1.12 (3H, d, *J* = 6.7 Hz, C20-C$\underline{H}_3$), 1.08 (9H, s, Si-C(C$\underline{H}_3$)$_3$), 1.07 (9H, s, Si-C(C$\underline{H}_3$)$_3$), 0.22 (3H, s, Si-C$\underline{H}_3$), 0.20 (3H, s, Si-C$\underline{H}_3$), 0.16 (3H, s, Si-C$\underline{H}_3$), 0.15 (3H, s, Si-C$\underline{H}_3$).

(2*R*,4*E*,6*E*,11*S*,12*S*,13*S*,14*E*,18*E*)-12,13-Bis((*tert*-butyldimethylsilyl)oxy)-2-((*R*,3*E*,5*E*)-6-iodo-4-methylhexa-3,5-dien-2-yl)-4-methyl-20-oxooxacycloicosa-4,6,14,18-tetraen-11-yl carbamate (213)

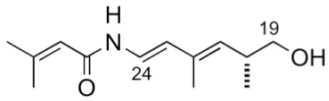


To a stirred solution of acid **212** (13.0 mg, 15.1 μmol) in toluene (1.0 mL) at rt was added Et_3N (42.0 μl, 0.302 mmol) and 2,4,6-trichlorobenzoyl chloride (35.0 μL, 0.226 mmol). After 1h, the reaction mixture was diluted with toluene (4.0 mL) and added over 3 h to a stirred solution of DMAP (74.0 mg, 0.604 mmol) in toluene (10.0 mL). The reaction mixture was stirred for 12 h and then quenched with $NaHCO_3$ (15.0 mL) solution. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by flash column chromatography (10% EtOAc/Hexanes) gave macrolactone **213** (9.0 mg, 71%) as a colourless oil.

***R**f* 0.44 (20% EtOAc/Hexane); $[\alpha]_D^{20}$ +1.2 (*c* 0.9, $CHCl_3$); **IR υ_{max}** (thin film/cm^{-1}) 3510, 3368, 3017, 2930, 2858, 1724, 1652, 1596, 1465, 1385, 1256, 1123, 1034, 973, 837, 776; **^{1}H NMR** (400 MHz, C_6D_6) δ 6.94-6.87 (1H, m_{obs}, H-3), 6.93 (1H, dd, *J* = 14.7, 0.7 Hz, H-23), 6.27 (1H, dd, *J* = 15.5, 11.1 Hz, H-15), 5.96-5.83 (2H, m_{obs}, H-2, H-16), 5.91 (1H, dd, *J* = 14.6, 0.5 Hz, H-24), 5.68-5.63 (2H, m, H-6, H-7), 5.53 (1H, ddd, *J* = 14.6, 9.3, 4.8 Hz, H-14), 5.19 (1H, dt, *J* = 10.3, 2.1 Hz, H-10), 5.12 (1H, ddd, *J* = 10.4, 7.6, 3.1 Hz, H-19), 4.97 (1H, d, *J* = 10.0 Hz, H-21), 4.21-4.16 (1H, m, H-8), 4.11 (1H, dd, *J* = 6.9, 1.8 Hz, H-9), 3.64 (2H, br s, N$\underline{H}_2$), 2.67-2.77 (1H, m, H-20), 2.37-2.27 (1H, m, H-13a), 2.18-2.09 (2H, m, H-18), 2.00-1.89 (4H, m, H-4, H-5), 1.89-1.86 (1H, m, H-13b), 1.86-1.81 (2H, m,

H-11), 1.80-1.66 (2H, m, H-12), 1.65 (3H, s, C17-C$\underline{H}_3$), 1.36 (3H, d, J = 1.2 Hz, C22-C$\underline{H}_3$), 1.10 (9H, s, Si-C(C$\underline{H}_3$)$_3$), 1.04 (9H, s, Si-C(C$\underline{H}_3$)$_3$), 0.95 (3H, d, J = 6.7 Hz, C20-C$\underline{H}_3$), 0.21 (3H, s, Si-C$\underline{H}_3$), 0.21 (3H, s, Si-C$\underline{H}_3$), 0.14 (3H, s, Si-C$\underline{H}_3$), 0.10 (3H, s, Si-C$\underline{H}_3$). **^{13}C NMR** (125 MHz, C_6D_6) δ 165.4, 156.1, 149.7, 147.4, 135.4, 133.0, 131.58, 131.39, 130.3, 129.2, 128.1 (obs), 127.5, 123.3, 78.3, 76.6, 75.5, 74.9, 74.3, 43.4, 37.5, 32.16, 31.98, 31.1, 30.2, 26.5, 26.4, 25.2, 18.71, 18.66, 17.2, 16.6, 12.1, -3.6, -3.7, -3.8, -4.2; **HRMS** (ES$^+$) calcd. for $C_{40}H_{68}INO_6Si_2Na$ $[M+Na]^+$ 864.3522, found 864.3528.

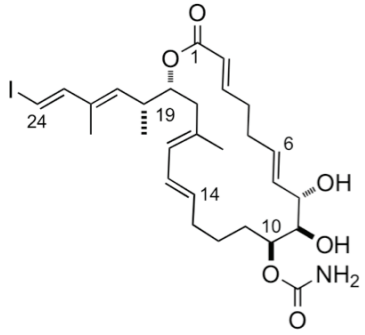
_N_-((1_E_,3_E_,5_R_)-6-Hydroxy-3,5-dimethylhexa-1,3-dien-1-yl)-3-methylbut-2-enamide (219)



To a mixture of vinyl iodide **178** (100 mg, 0.396 mmol), amide **218** (78.6 mg, 0.793 mmol), flame-dried K_2CO_3 (328 mg, 2.37 mmol) and CuI (113 mg, 0.594 mmol) in THF (20.0 mL) at rt was added *N,N'*-dimethylethylenediamine (128 µL, 1.18 mmol). The reaction mixture was stirred for 1 h before it was concentrated under reduced pressure. The resulting residue was diluted with EtOAc (10.0 mL), filtered through a pad of Celite®, washed with EtOAc (10.0 mL) and concentrated under reduced pressure. Purification by flash column chromatography afforded enamide **219** (50.0 mg, 63%) as a colourless oil, in 5:1 *E*:*Z* ratio.

R_f_ 0.56 (10% EtOAc/Hexane); **IR υ_{max}** (thin film/cm^{-1}) 3425, 2982, 2935, 1718, 1655, 1315, 1272, 1157, 1041, 981; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 (1H, d, J = 10.4, N-$\underline{H}$), 6.99 (1H, dd, J = 14.4, 10.5 Hz, H-23), 5.81 (1H, dd, J = 14.5, 0.6 Hz, H-24), 5.60 (1H, dt, J = 2.6, 1.3 Hz, H-27), 5.06 (1H, d, J = 9.5 Hz, H-21), 3.48-3.42 (1H, m, H-19a), 3.38-3.32 (1H, m, H-19b), 2.74-2.66 (1H, m, H-20), 2.17 (3H, d, J = 1.2 Hz, H-29), 1.84 (3H, d, J = 1.2 Hz, -CH_3), 1.77 (3H, d, J = 1.2, C22-CH_3), 0.93 (3H, d, J = 6.7 Hz, C20-CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.0, 153.9, 133.9, 131.9, 121.5, 117.8, 117.5, 67.8, 35.7, 27.5, 20.1, 17.2, 13.0; **HRMS** (ES$^+$) calcd. for $C_{13}H_{22}NO_2$ $[M+H]^+$ 224.1645, found 224.1646.

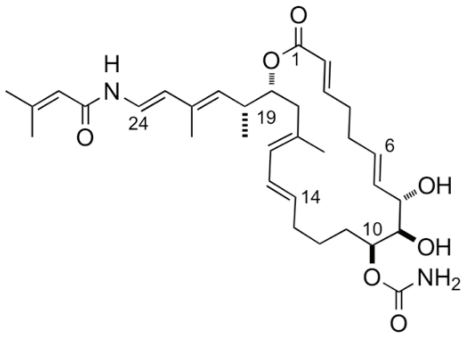
(2*R*,4*E*,6*E*,11*S*,12*R*,13*S*,14*E*,18*E*)-12,13-Dihydroxy-2-((*R*,3*E*,5*E*)-6-iodo-4-methylhexa-3,5-dien-2-yl)-4-methyl-20-oxooxacycloicosa-4,6,14,18-tetraen-11-yl carbamate (214)



To a solution of bis-TBS-ether **213** (9.00 mg, 10.7 μmol) in THF (1.0 mL) at 0 ºC was added TBAF (54.0 μL, 1 M soln. in THF, 54.0 μmol). The reaction was stirred for 2 h, quenched with cold water (1.0 mL) and the layers were separated. The aqueous phase was extracted with EtOAc (3 × 5 mL) and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by flash column chromatography (50-100% EtOAc/Pet.Ether) provided diol **214** (5.5 mg, 85%) as a white flakes.

***R**f* 0.39 (5% MeOH/CH_2Cl_2); $[\alpha]_D^{20}$ +9.6 (*c* 0.5, $CHCl_3$); **IR** υ_{max} (thin film/cm^{-1}) 3432, 2923, 2851, 1713, 1651, 1461, 1391, 1276, 1060, 1020, 972; **^{1}H NMR** (500 MHz, C_6D_6) δ 6.93 (1H, d, *J* = 14.5 Hz, H-23), 6.86 (1H, dt, *J* = 15.6, 5.9 Hz, H-3), 6.33 (1H, dd, *J* = 14.9, 11.2 Hz, H-15), 5.96-5.92 (1H, m, H-16), 5.92 (1H, d, *J* = 14.7 Hz, H-24), 5.83 (1H, d, *J* = 15.8 Hz, H-2), 5.57 (1H, dt, *J* = 14.6, 5.4 Hz, H-6), 5.47-5.39 (2H, m, H-7, H-14), 5.19-5.13 (1H, m, H-19), 5.00-4.93 (2H, m, H-10, H-21), 4.17-3.98 (2H, br s, N$\underline{H}_2$), 3.91 (1H, t, *J* = 7.0 Hz, H-8), 3.68 (1H, br s, H-9), 2.69 (1H, dt, *J* = 10.1, 7.0 Hz, H-20), 2.30-2.22 (1H, m, H-13a), 2.12-2.18 (2H, m, H-18), 1.91-1.97 (1H, m, H-13b), 1.89-1.77 (4H, m, H-4, H-5), 1.77-1.71 (1H, m, H-11a), 1.73 (3H, s, C17-C$\underline{H}_3$), 1.71-1.68 (1H, m, H-11b), 1.67-1.62 (1H, m, H-12a), 1.35 (3H, d, *J* = 0.9 Hz, C22-C$\underline{H}_3$), 1.34-1.28 (1H, m, H-12b), 0.92 (3H, d, *J* = 6.8 Hz, C20-C$\underline{H}_3$); **^{13}C NMR** (125 MHz, C_6D_6) δ 165.6, 157.0, 149.5, 147.9, 135.3, 135.1, 132.3, 131.93, 131.90, 130.2, 128.4, 127.3, 122.9, 75.9, 75.4, 74.82, 74.72, 72.8, 42.8, 37.5, 31.8, 31.6, 30.3, 27.1, 24.7, 16.9, 16.6, 12.0; **HRMS** (ES^+) calcd. for $C_{28}H_{40}INO_6Na$ $[M+Na]^+$ 636.1785, found 636.1787.

9,10-bis-*epi*-palmerolide (3b)



To a mixture of vinyl iodide **214** (4.0 mg, 6.52 μmol), amide **218** (1.9 mg, 19.5 μmol), K_2CO_3 (4.5 mg, 32.6 μmol, flame-dried) and CuI (2.5 mg, 13.0 μmol) in degassed DMF (0.6 mL) was added *N,N'*-dimethylethylenediamine (19.5 μL, 0.01 M soln. in DMF, 19.5 μmol) at rt. The reaction mixture was stirred for 1 h before it was diluted with EtOAc (5.0 mL), filtered through a pad of Celite®, washed with EtOAc (5.0 mL) and concentrated under reduced pressure. Purification by flash column chromatography (2% MeOH/CH_2Cl_2) afforded enamide **3** (2.0 mg, 53%) as a white solid and recovered starting material (1.5 mg, 39%).

R_f 0.31 (5% MeOH/CH_2Cl_2); $[\alpha]_D^{20}$ -19.5 (*c* 0.2, MeOH); **IR υ_{max}** (thin film/cm^{-1}) 3319, 2943, 2831, 1730, 1717, 1609, 1514, 1449, 1358, 1165, 1099, 1022, 783;

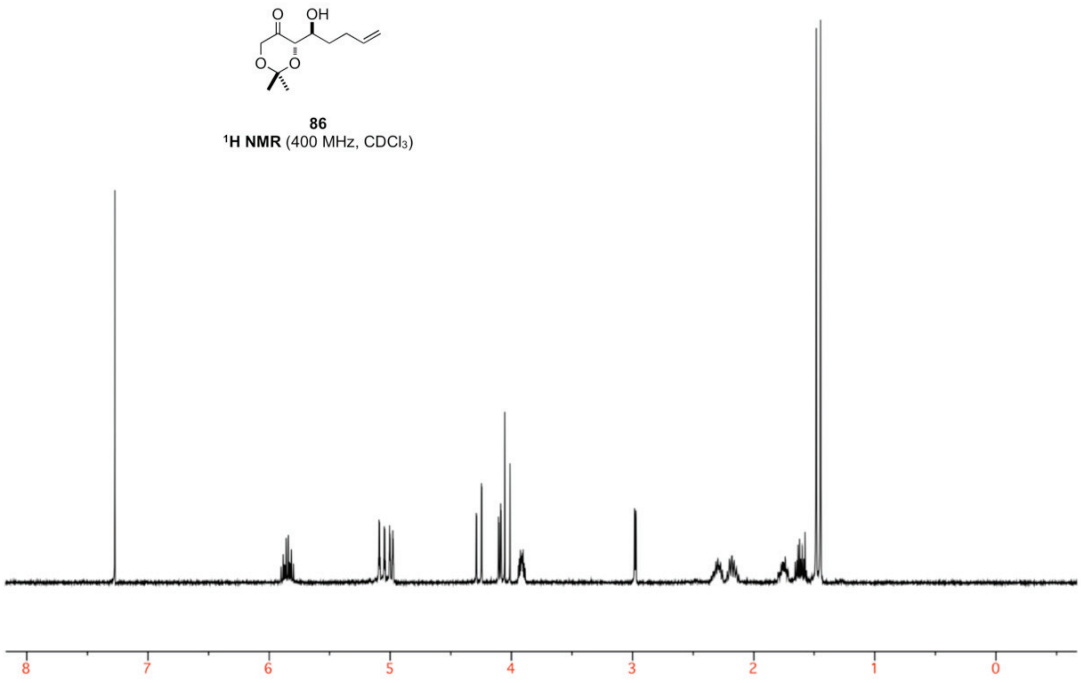
^{1}H NMR (500 MHz; CD_3CN) δ 8.14 (1H, d, *J* = 10.5 Hz, NH), 6.93 (1H, dd, *J* = 14.5, 10.6 Hz, H-24), 6.84-6.78 (1H, m, H-3), 6.20 (1H, dd, *J* = 14.7, 10.9 Hz, H-15), 5.87 (1H, d, *J* = 14.6 Hz, H-23), 5.76 (1H, d, *J* = 10.7 Hz, H-16), 5.71 (1H, d, *J* = 15.7 Hz, H-2), 5.62 (1H, s, H-2'), 5.49-5.46 (1H, m, H-6), 5.46-5.42 (1H, m, H-14), 5.36 (1H, dd, *J* = 15.2, 8.0 Hz, H-7), 5.20 (1H, d, *J* = 9.7 Hz, H-21), 5.05-5.16 (2H, m, NH_2), 4.94 (1H, ddd, *J* = 10.5, 7.7, 2.4 Hz, H-19), 4.52 (1H, dt, *J* = 10.4, 3.1 Hz, H-10), 3.75-3.70 (1H, m, H-8), 3.47-3.43 (1H, m, H-9), 3.17 (1H, d, *J* = 4.0 Hz, C9-OH), 3.11 (1H, d, *J* = 3.3 Hz, C8-OH), 2.78 (1H, dt, *J* = 9.85, 6.92 Hz, H-20), 2.45-2.37 (1H, m, H-4a), 2.33-2.24 (2H, m, H-18a, H-5a), 2.20 (1H, dd, *J* = 14.2, 11.1 Hz, H-18b), 2.16 (3H, s, H-4'), 2.18-2.12 (2H, m, H-4b, H-5b), 1.93-1.84 (2H, m, H-13), 1.86 (3H, s, H-5'), 1.74 (3H, s, C22-CH_3), 1.68 (3H, s, C17-CH_3), 1.54-1.45 (1H, m, H-11a), 1.43-1.36 (2H, m, H-11b, H-12a), 1.17-1.10 (1H, m, H-12b), 0.94 (3H, d, *J* = 6.7 Hz, C20-CH_3).

^{1}H NMR (500 MHz; DMSO) δ 9.88 (1H, d, *J* = 10.3 Hz, NH), 6.85 (1H, dd, *J* = 14.0, 10.4 Hz, H-24), 6.78 (1H, dt, *J* = 15.6, 7.4 Hz, H-3), 6.48-6.28 (2H, m, NH_2), 6.15 (1H, dd, *J* =

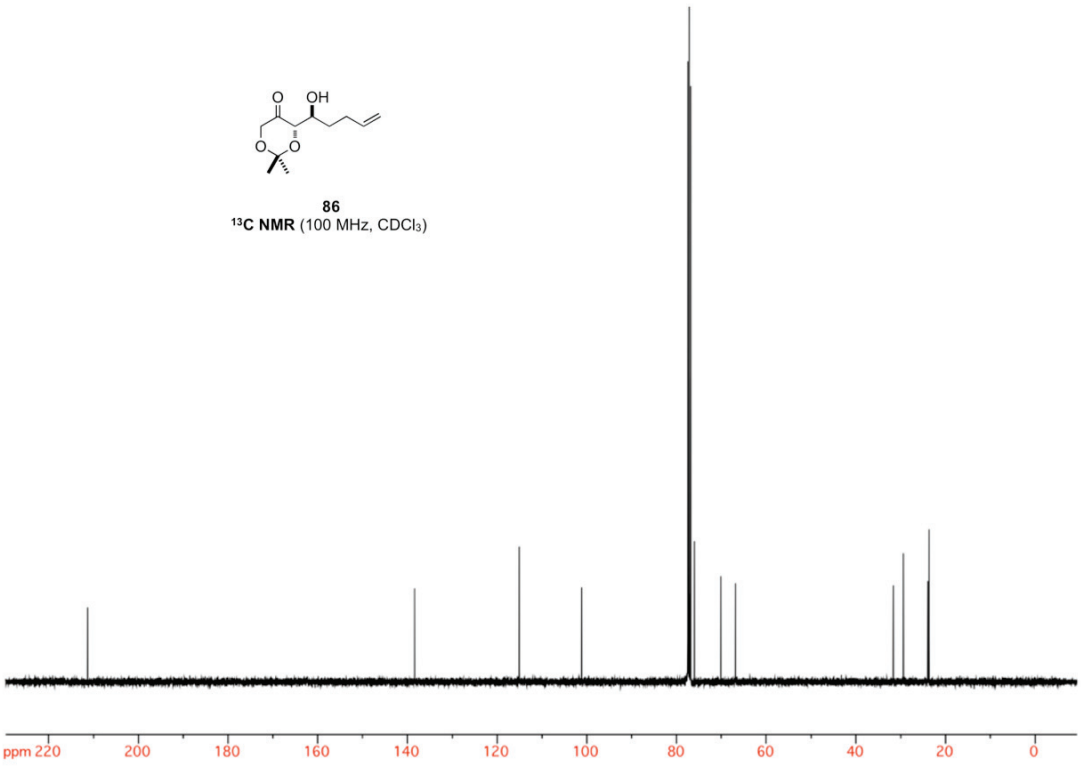
14.1, 11.3 Hz, H-15), 5.85 (1H, d, *J* = 14.5 Hz, H-23), 5.69-5.76 (3H, m, H-2, H-16, H-2'), 5.46-5.35 (2H, m, H-6, H-14), 5.35-5.27 (1H, m, H-7), 5.16 (1H, d, *J* = 9.5 Hz, H-21), 4.87 (1H, t, *J* = 8.5 Hz, H-19), 4.77 (1H, s, C9-O<u>H</u>), 4.68 (1H, s, C8-O<u>H</u>), 4.42 (1H, d, *J* = 10.3 Hz, H-10), 3.56 (1H, obs, H-9), 3.46 (1H, obs, H-8), 2.75 (1H, m, H-20), 2.14-2.25 (2H, m, H-18), 2.12 (3H, s, H-5'), 2.26-2.22 (1H, m, H-5a), 2.21 (2H, m, H-12), 2.08-1.93 (3H, m, H-4, H-5b), 1.83 (3H, s, H-4'), 1.82-1.78 (2H, m, H-13), 1.68 (3H, s, C22-C<u>H</u>$_3$), 1.64 (3H, s, C17-C<u>H</u>$_3$), 1.57-1.49 (1H, m, H-11a), 1.49-1.42 (1H, m, H-11b), 0.91 (3H, d, *J* = 6.5 Hz, C20-C<u>H</u>$_3$).

^{13}C NMR (HSQC, HMBC, CD_3CN) δ 166.2, 164.2, 164.4, 154.1, 142.4, 133.2, 132.6, 132.5, 130.9, 130.3, 130.1, 128.6, 127.9, 123.3, 122.3, 118.1, 117.2, 76.0, 75.3, 75.26, 74.2, 43.1, 37.8, 32.4, 31.8, 30.7, 27.25, 26.1, 24.8, 19.8, 17.4, 16.2, 12.9; **HRMS** (ES^+) calcd. for $C_{33}H_{48}N_2NaO_7$ $[M+Na]^+$ 607.3359, found 607.3364.

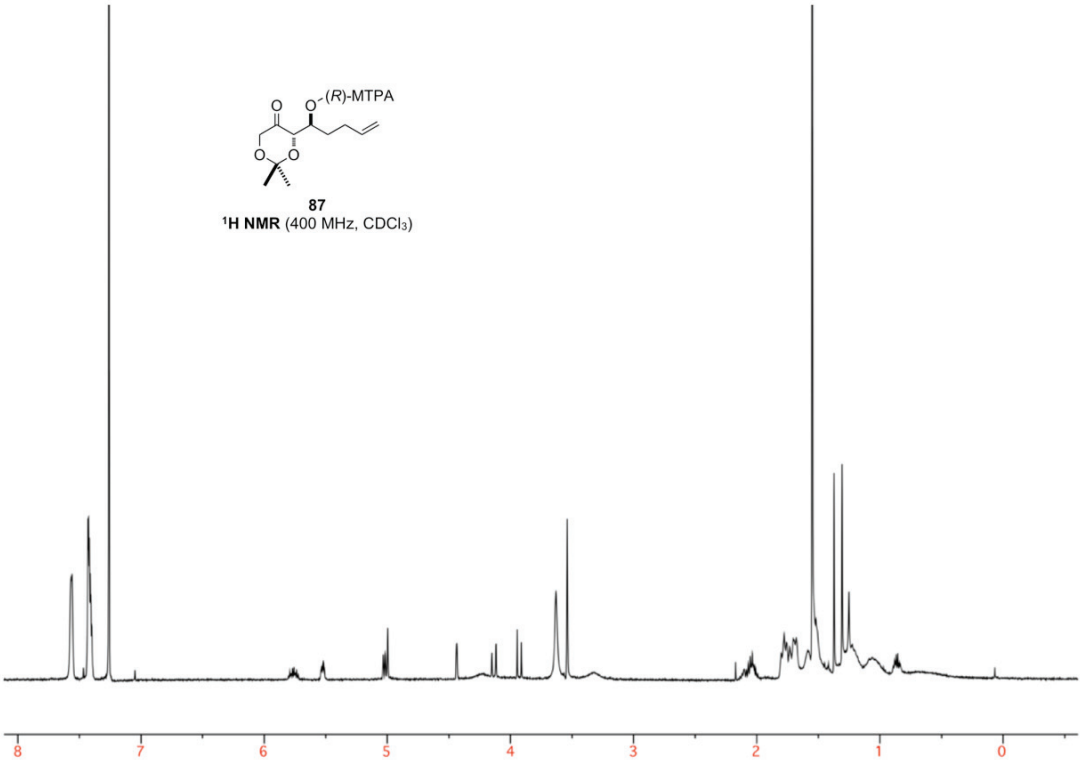
Appendix: Selected ^{1}H and ^{13}C NMR spectra

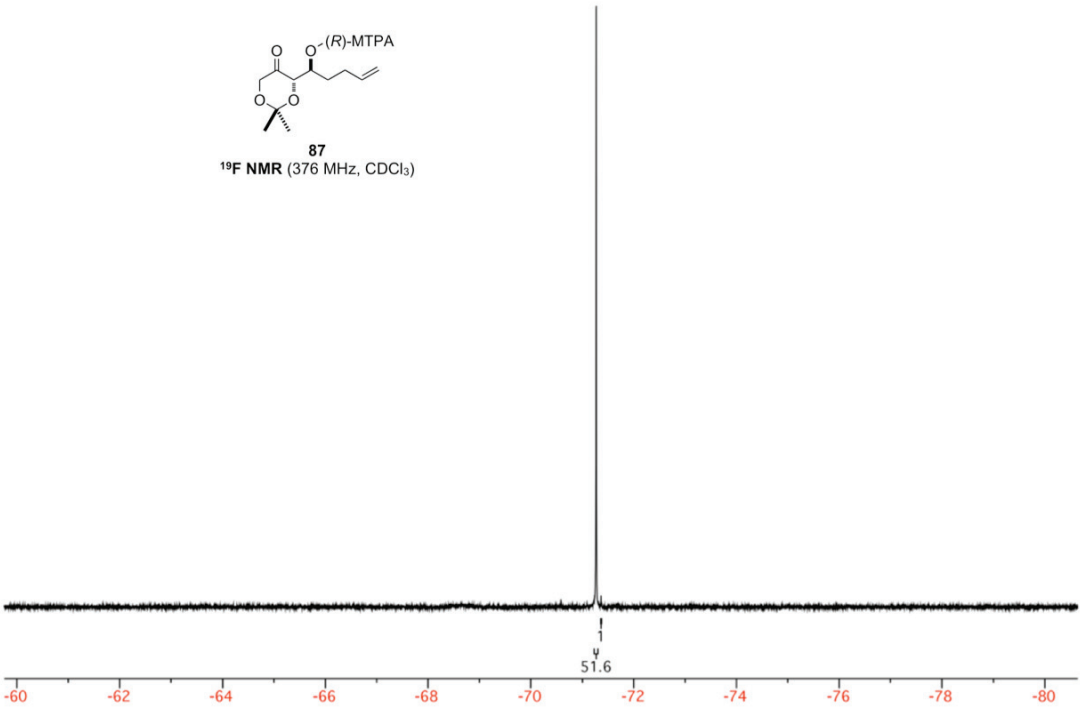


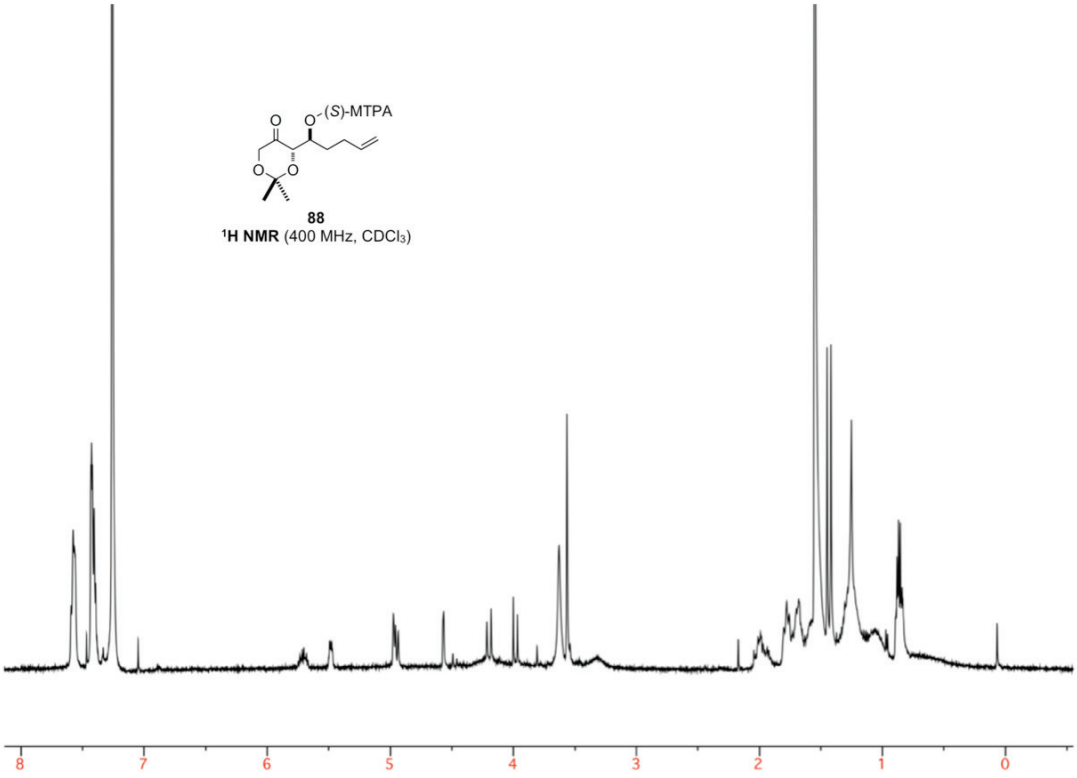
86
^{1}H NMR (400 MHz, $CDCl_3$)

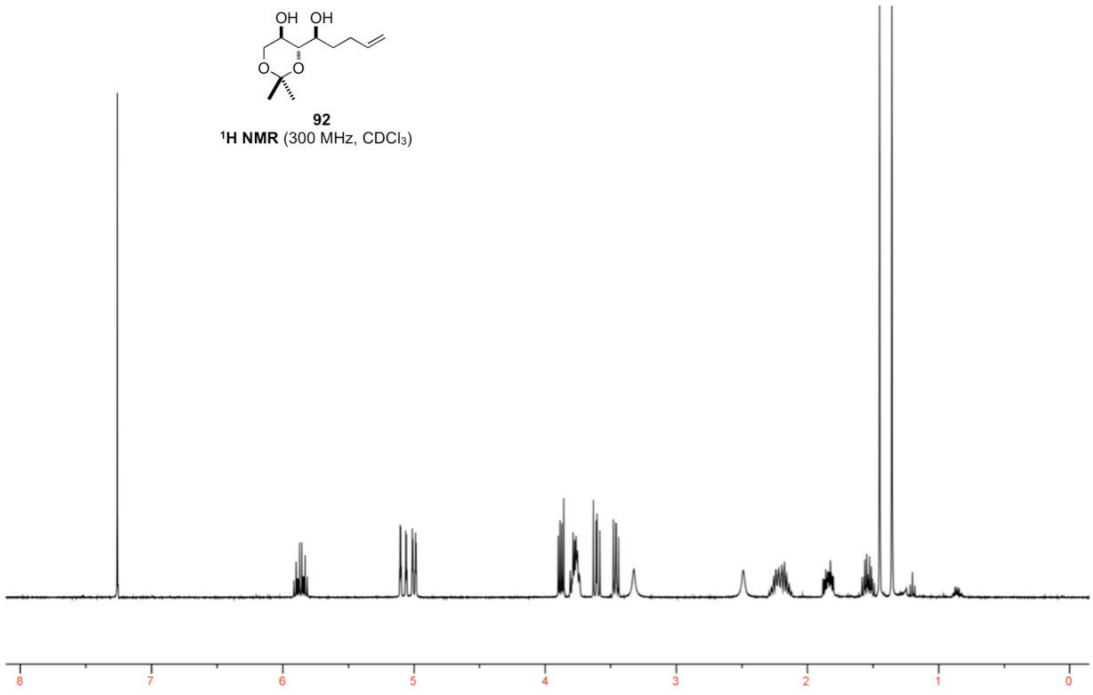


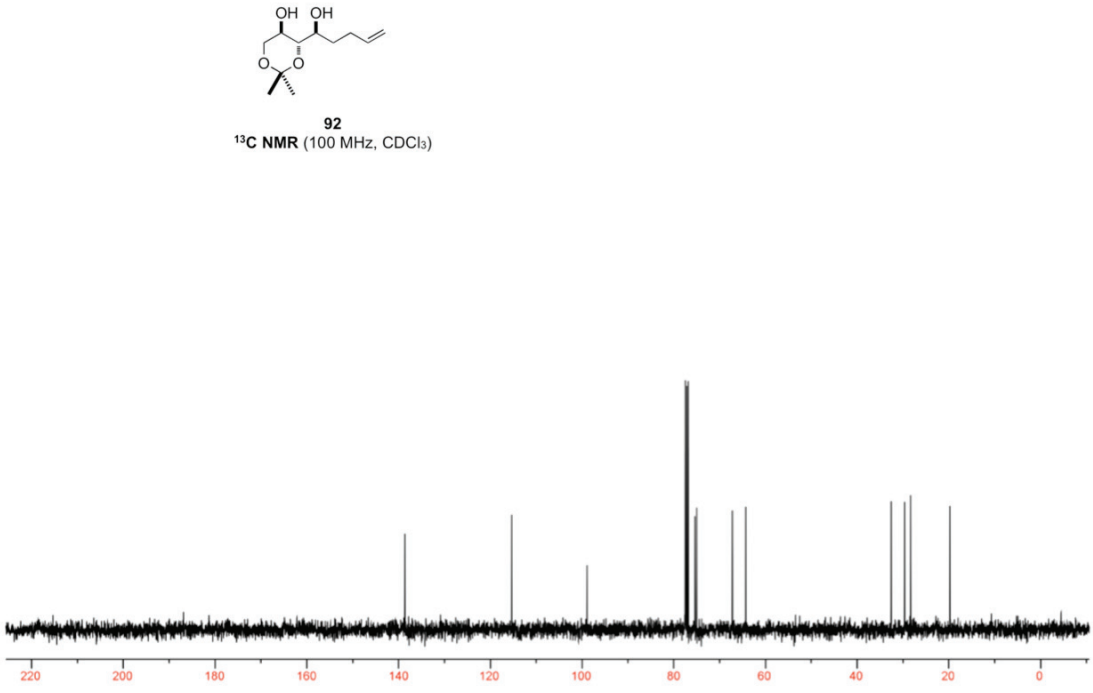
86
^{13}C NMR (100 MHz, $CDCl_3$)

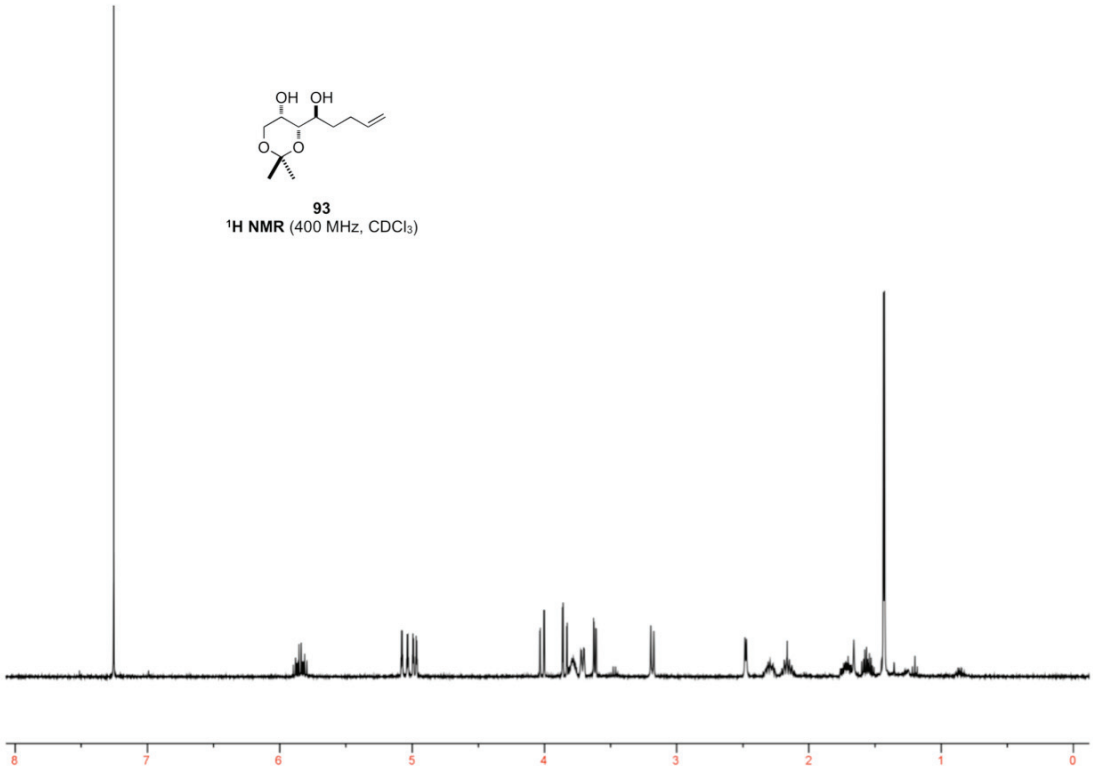

(R)-MTPA
87
¹H NMR (400 MHz, CDCl₃)
8
7
6
5
4
3
2
1
0


(R)-MTPA
87
¹⁹F NMR (376 MHz, CDCl₃)
1
51.6
-60
-62
-64
-66
-68
-70
-72
-74
-76
-78
-80

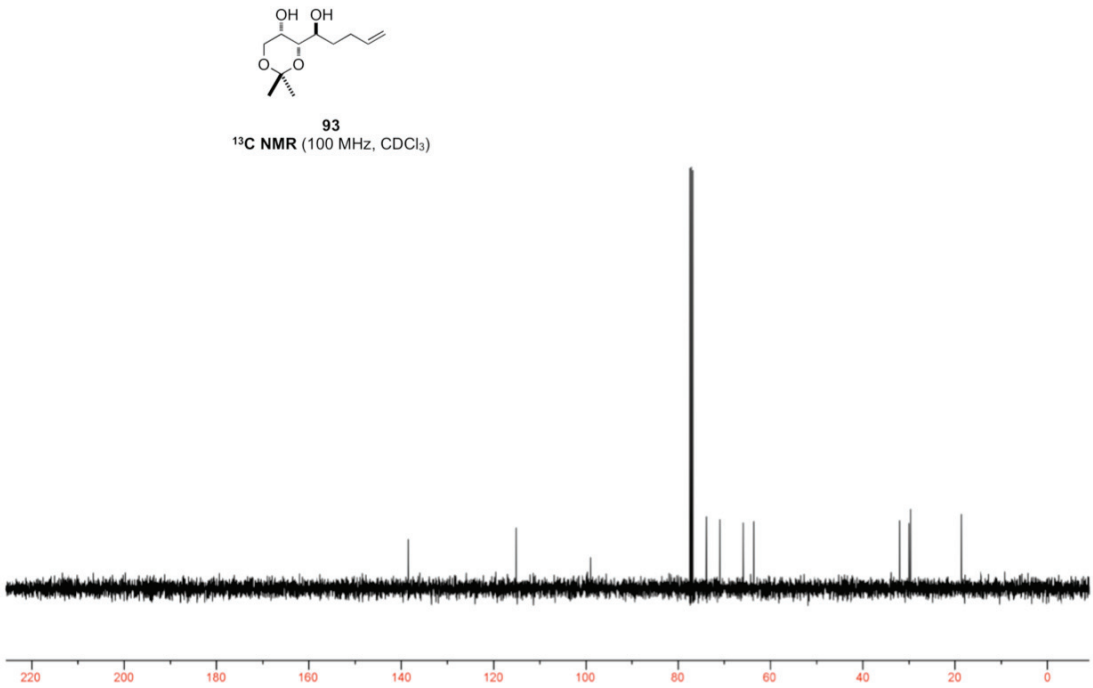

(S)-MTPA
88
¹H NMR (400 MHz, CDCl₃)
8
7
6
5
4
3
2
1
0


OH
OH
O
O
92
¹H NMR (300 MHz, CDCl₃)
8
7
6
5
4
3
2
1
0

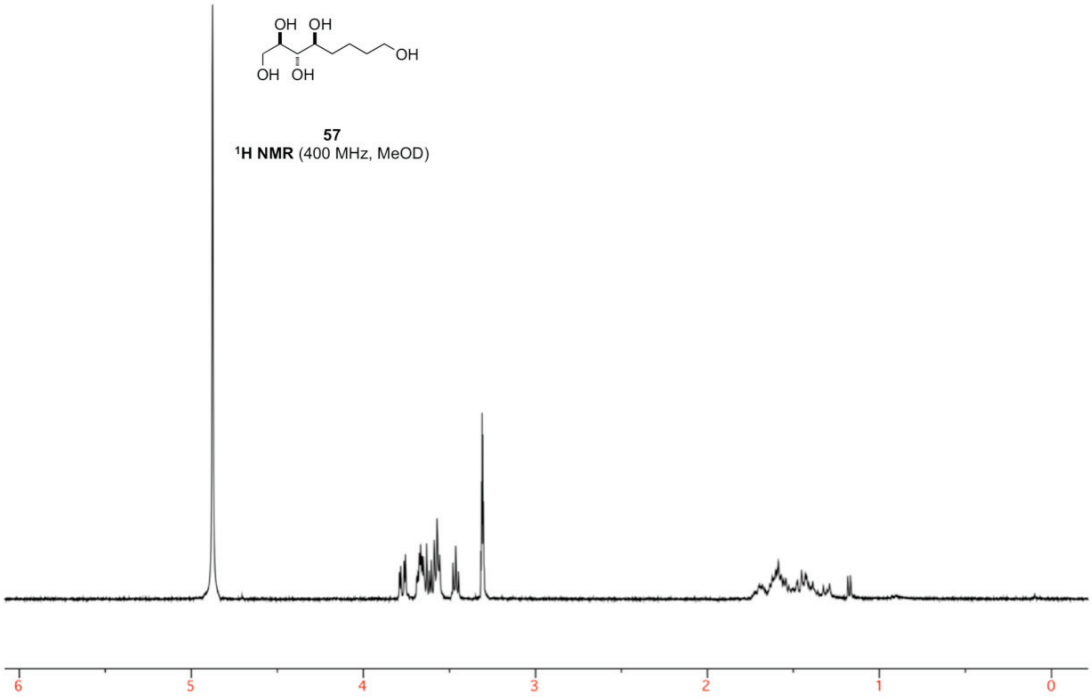

OH
OH
O
O
92
¹³C NMR (100 MHz, CDCl₃)
220
200
180
160
140
120
100
80
60
40
20
0

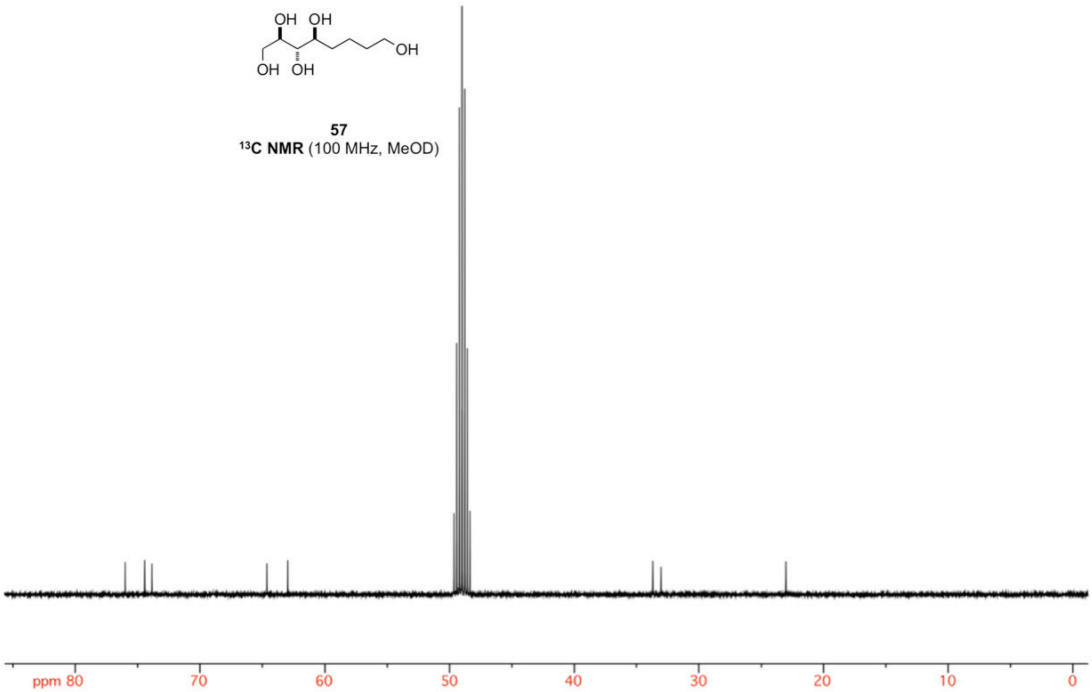


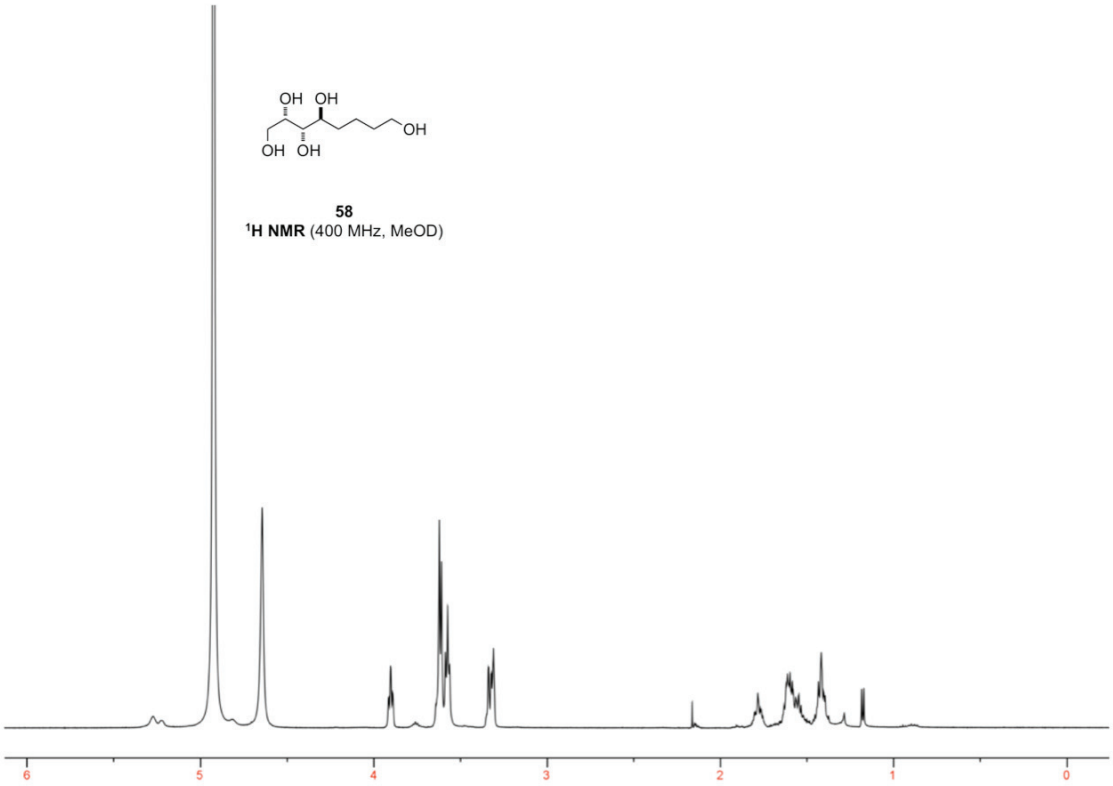
93
^{1}H NMR (400 MHz, $CDCl_3$)



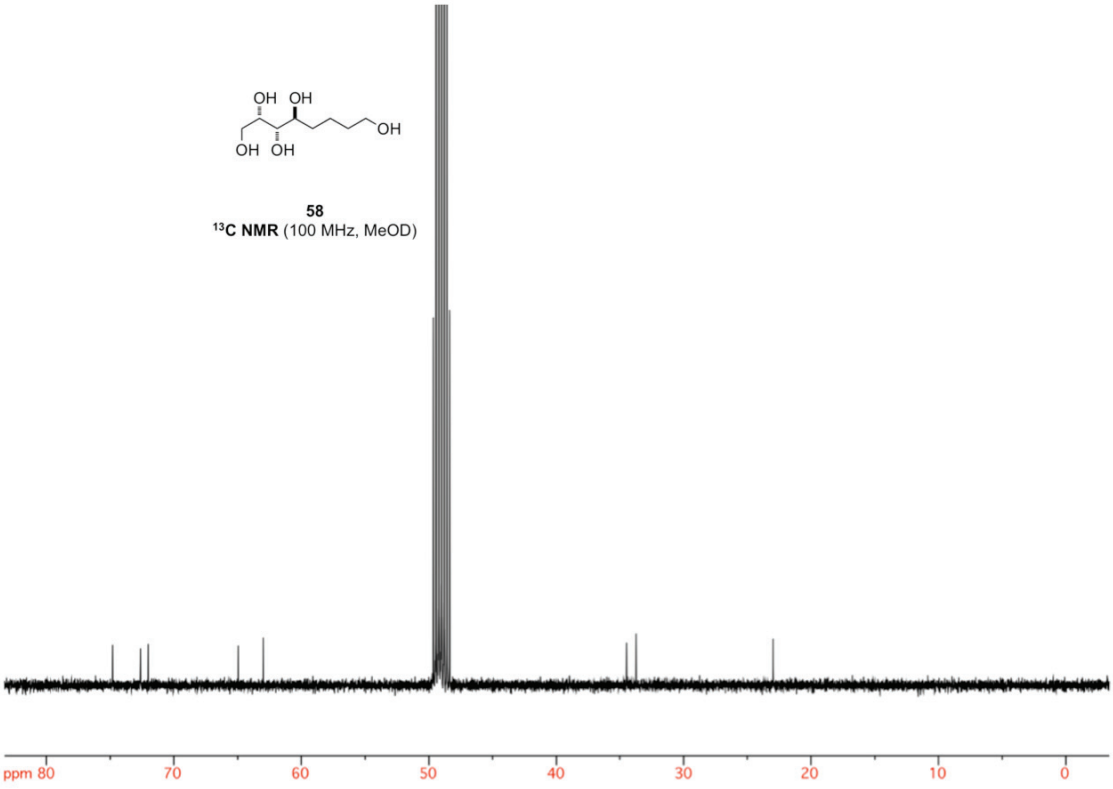
93
^{13}C NMR (100 MHz, $CDCl_3$)


OH OH
OH
OH OH
57
¹H NMR (400 MHz, MeOD)
6
5
4
3
2
1
0

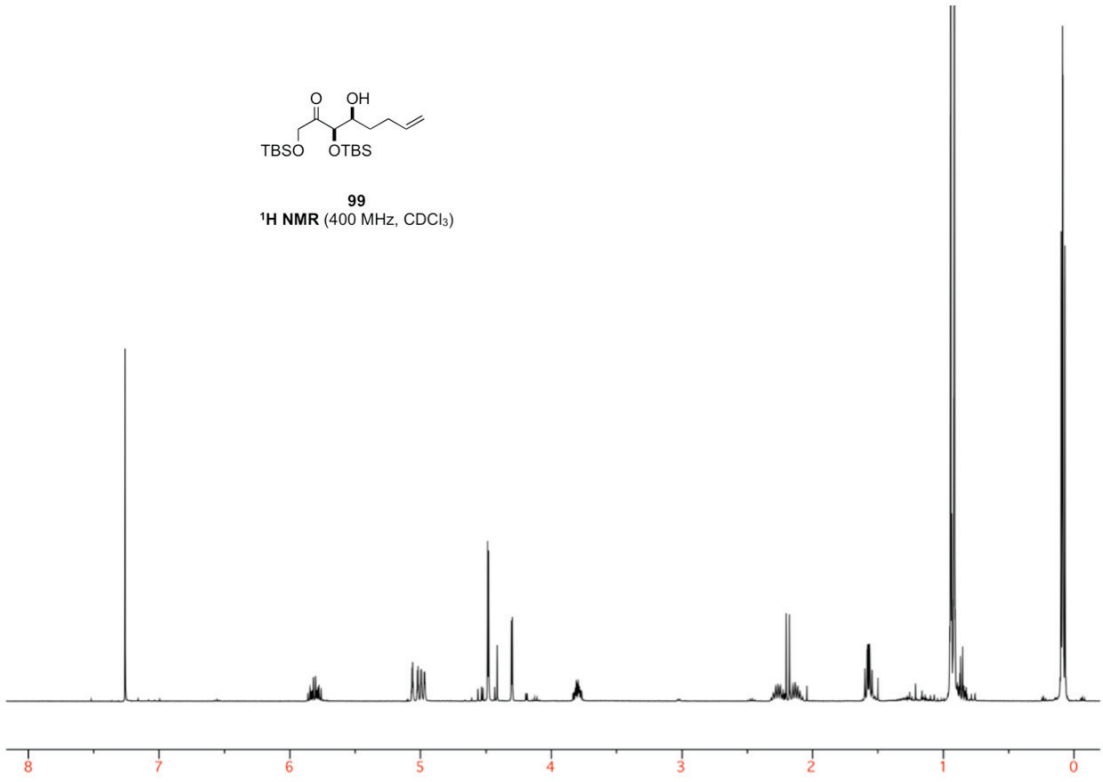

OH OH
OH
OH OH
57
¹³C NMR (100 MHz, MeOD)
ppm 80
70
60
50
40
30
20
10
0

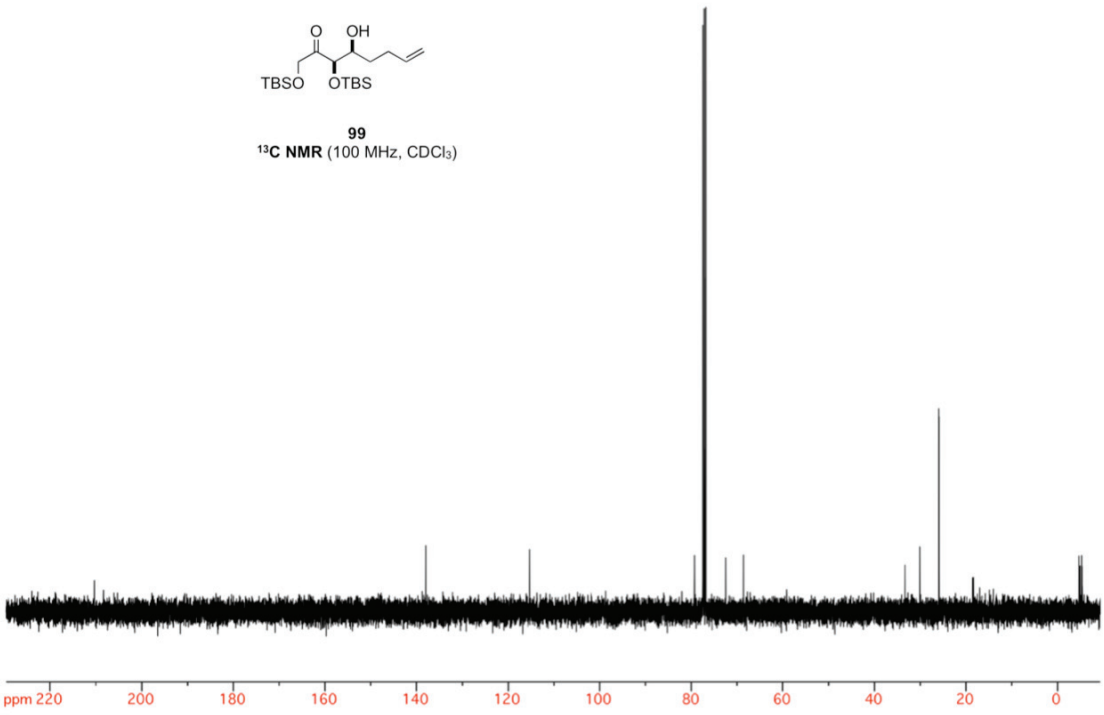


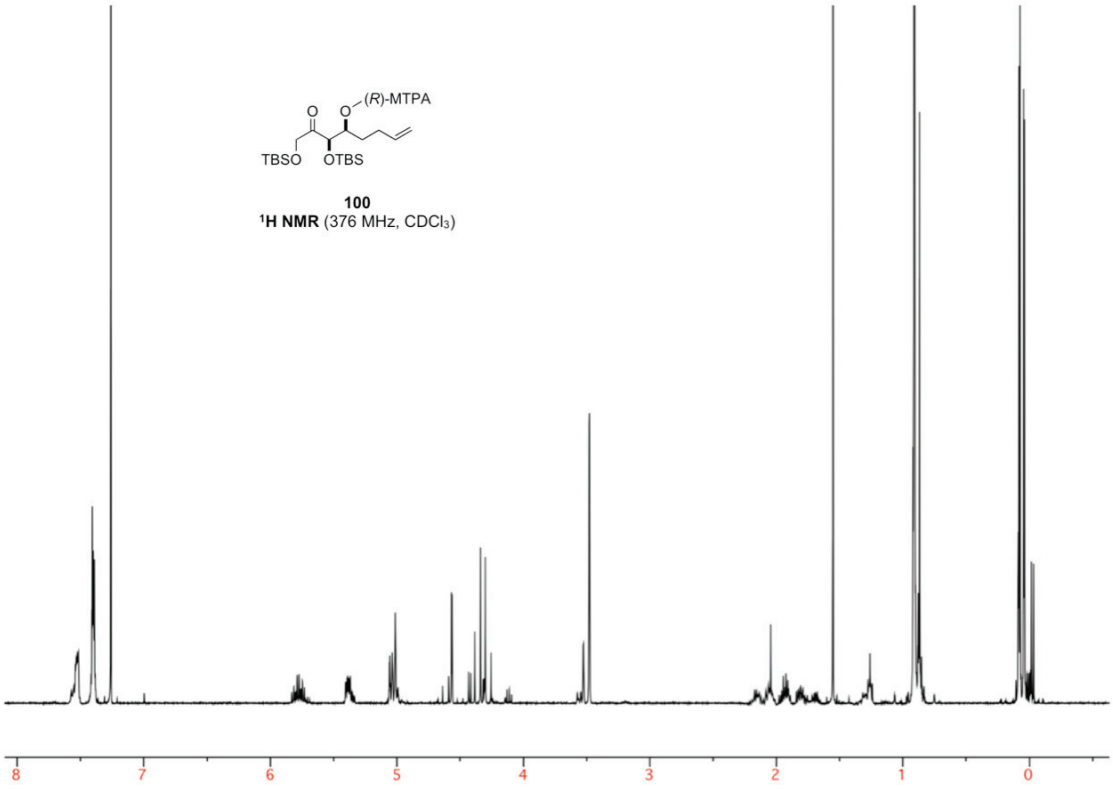
58
^{1}H NMR (400 MHz, MeOD)



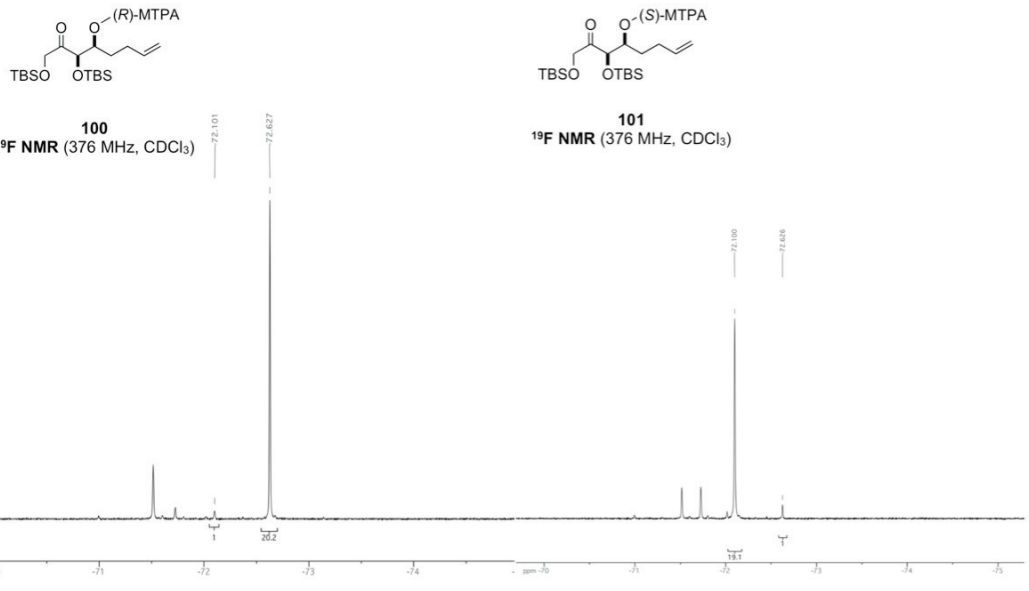
58
^{13}C NMR (100 MHz, MeOD)


O
OH
TBSO
OTBS
99
¹H NMR (400 MHz, CDCl₃)
8
7
6
5
4
3
2
1
0


O
OH
TBSO
OTBS
99
¹³C NMR (100 MHz, CDCl₃)
ppm 220
200
180
160
140
120
100
80
60
40
20
0

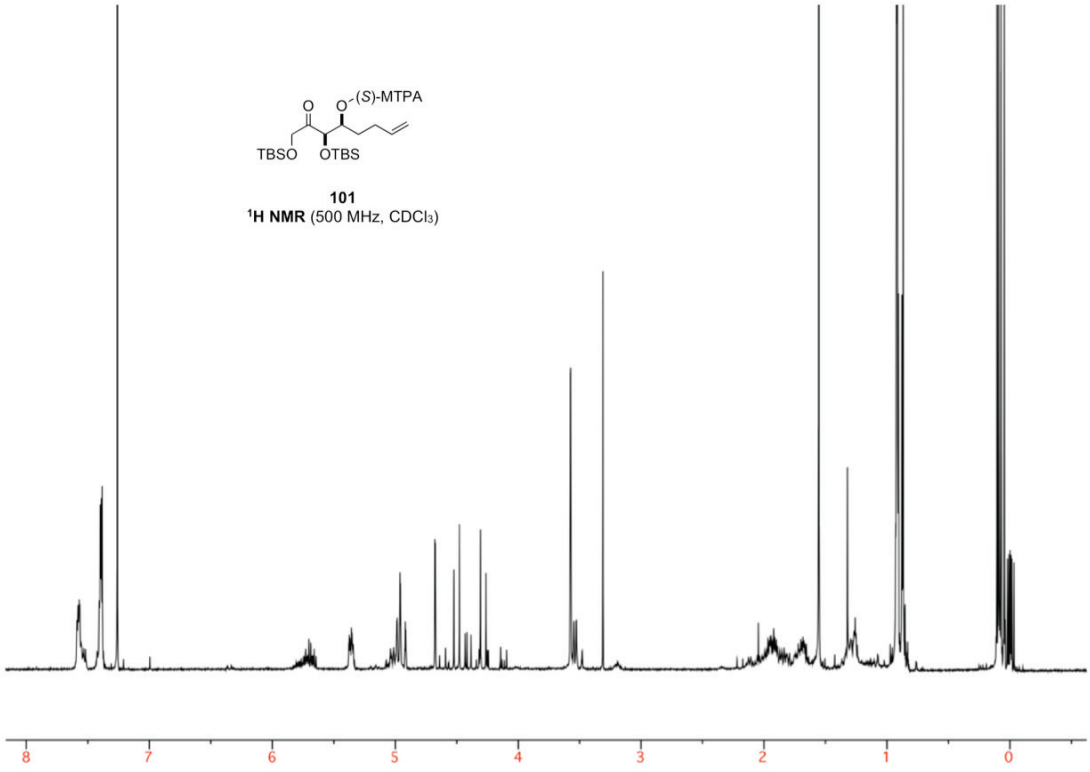


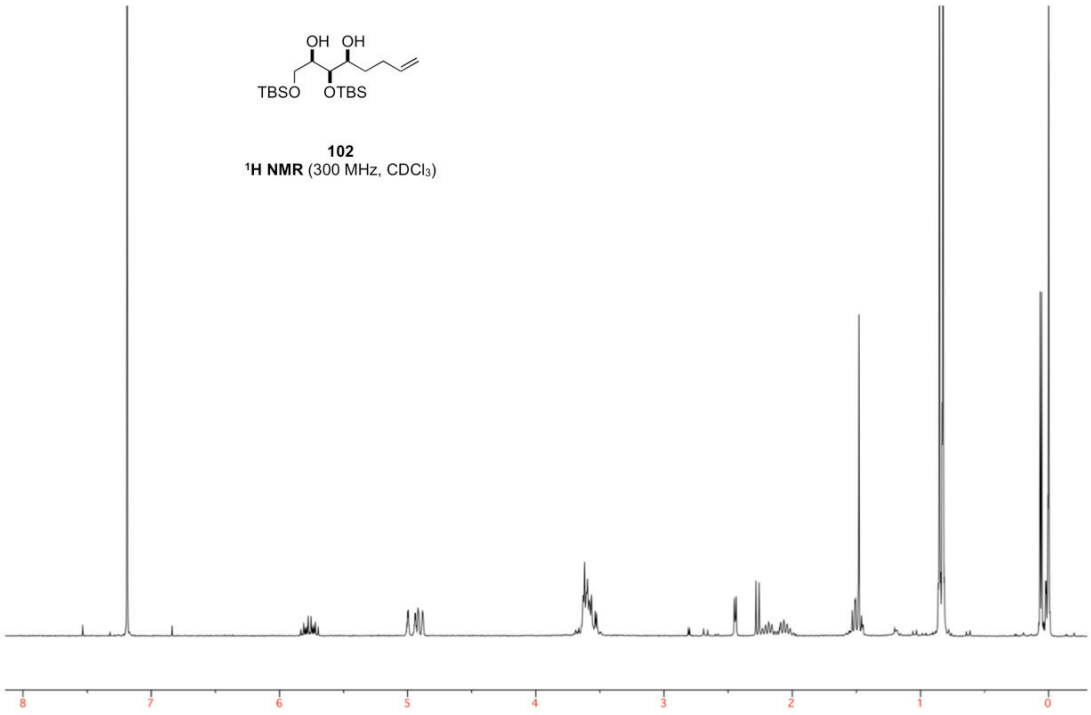
100
^{1}H NMR (376 MHz, $CDCl_3$)



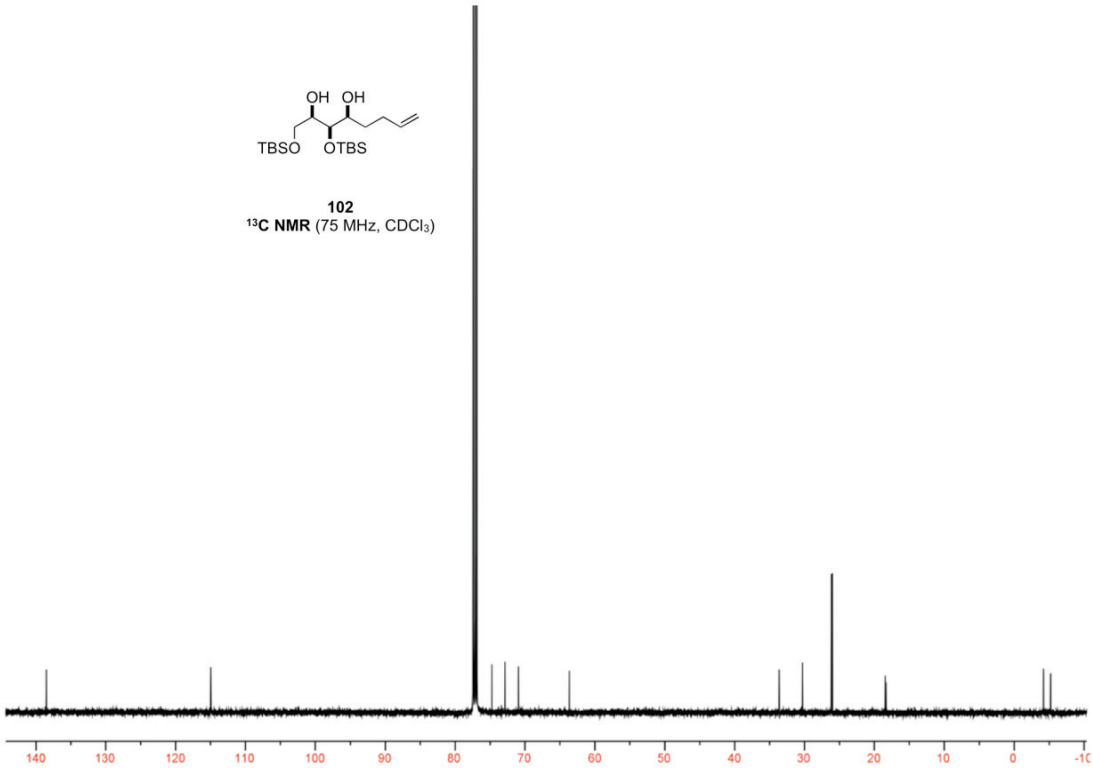
100
^{19}F NMR (376 MHz, $CDCl_3$)

101
^{19}F NMR (376 MHz, $CDCl_3$)

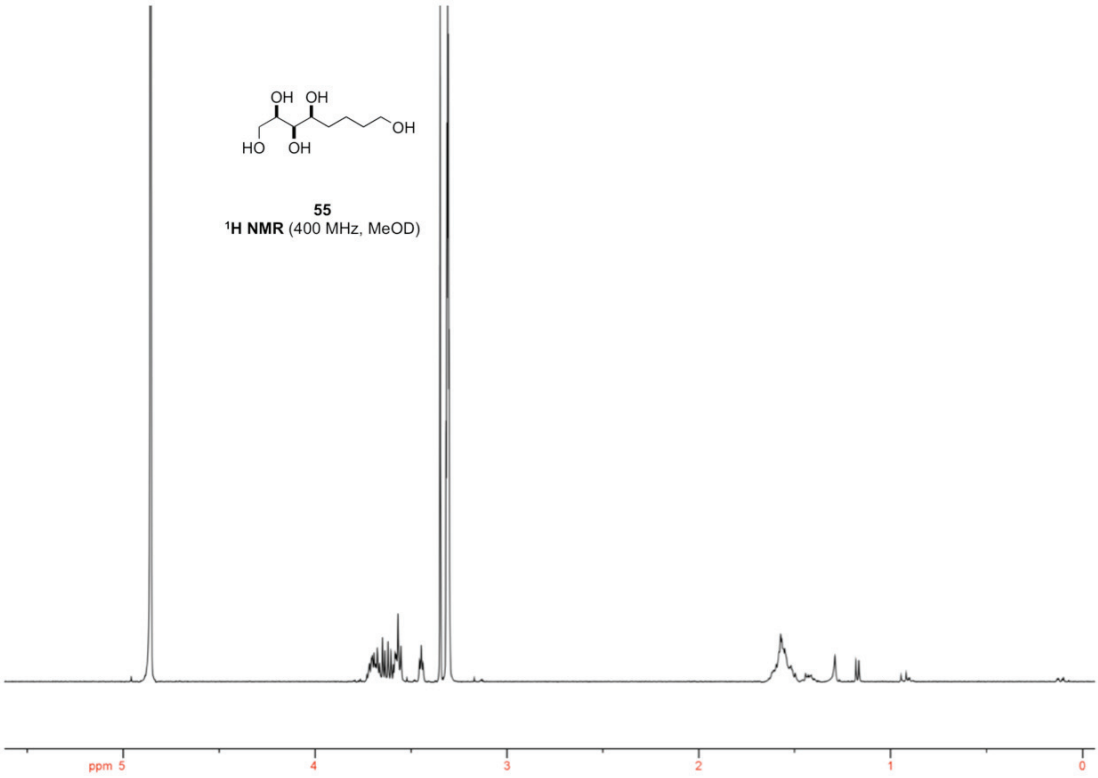

(S)-MTPA
TBSO
OTBS
101
¹H NMR (500 MHz, CDCl₃)
8
7
6
5
4
3
2
1
0



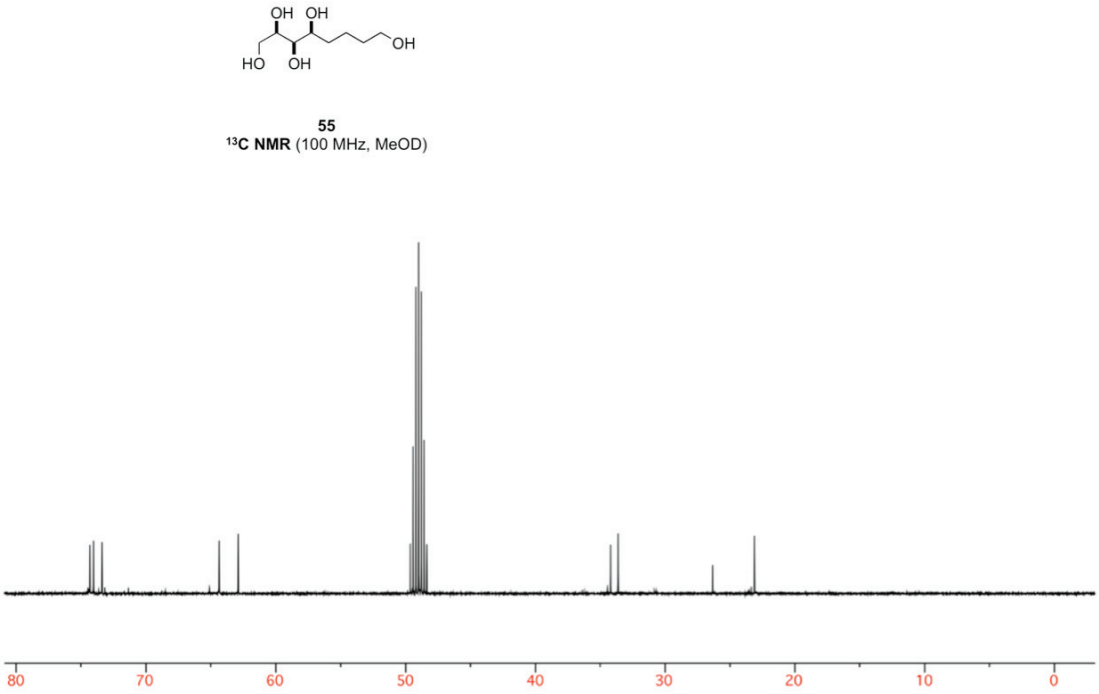
102
^{1}H NMR (300 MHz, $CDCl_3$)



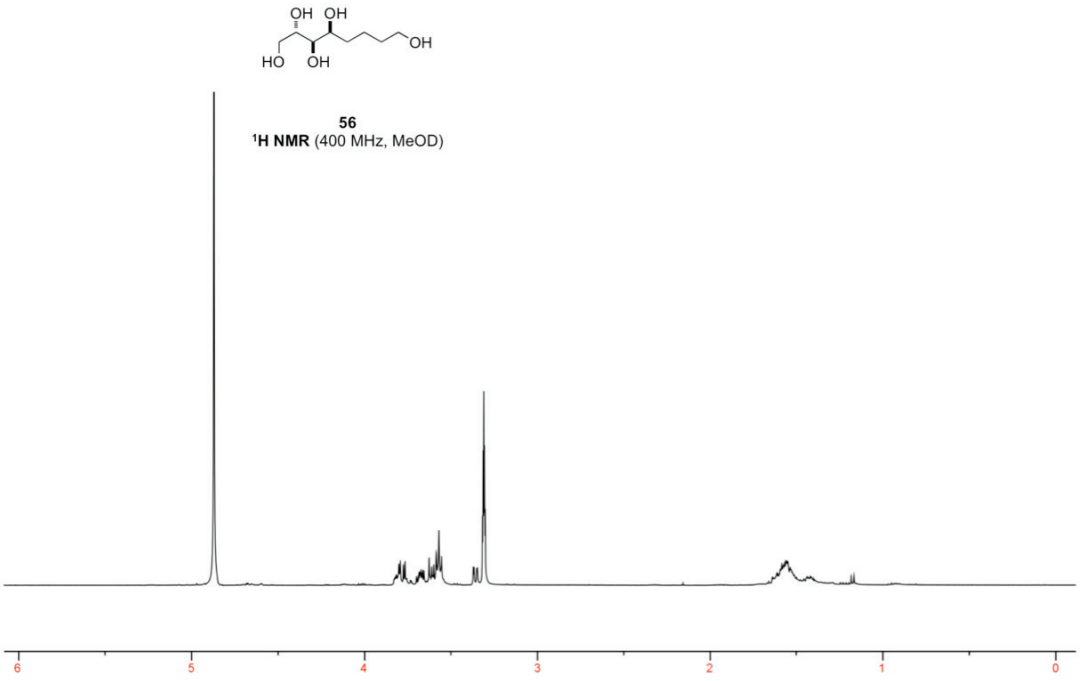
102
^{13}C NMR (75 MHz, $CDCl_3$)

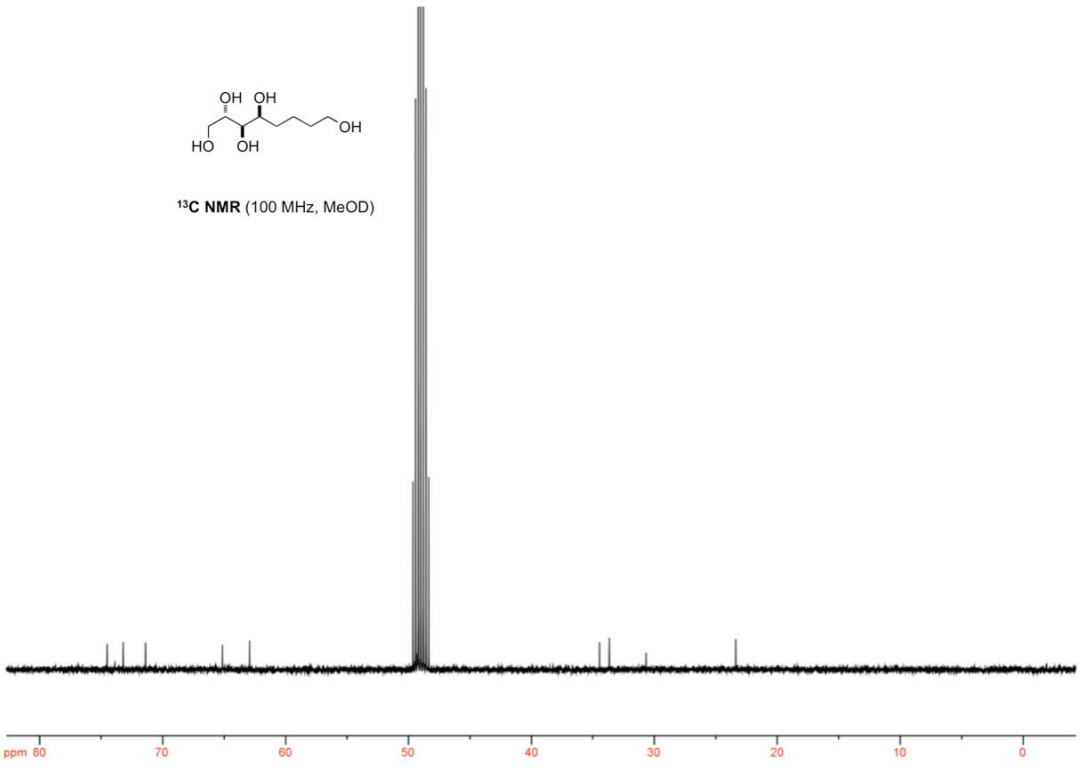


55
^{1}H NMR (400 MHz, MeOD)

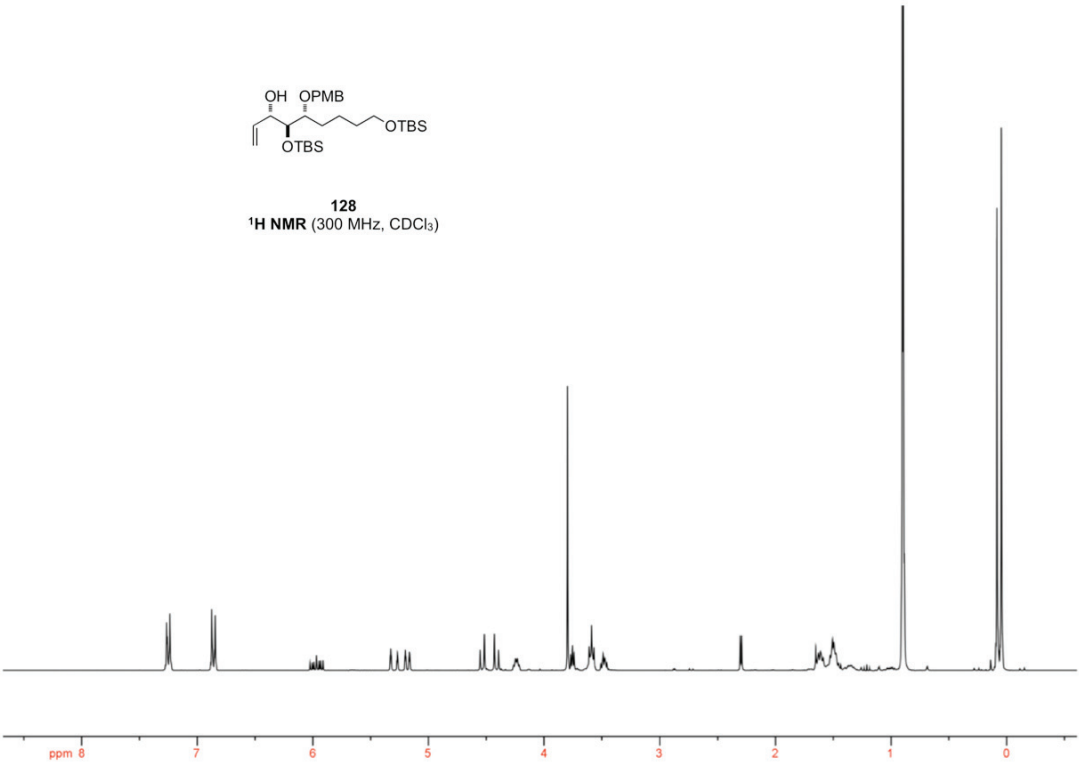


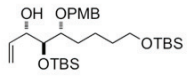
55
^{13}C NMR (100 MHz, MeOD)


OH OH
HO OH
OH
56
¹H NMR (400 MHz, MeOD)
6
5
4
3
2
1
0

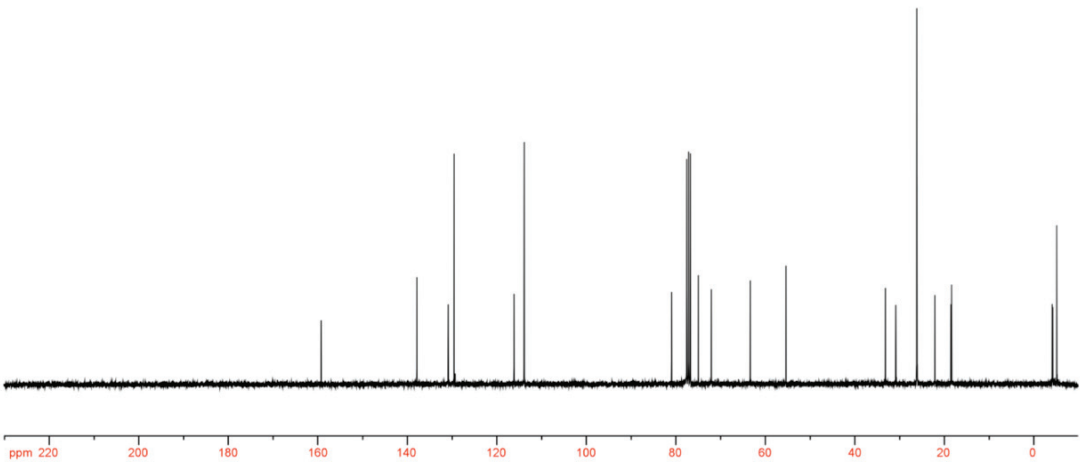

OH OH
HO OH
OH
¹³C NMR (100 MHz, MeOD)
ppm 80
70
60
50
40
30
20
10
0

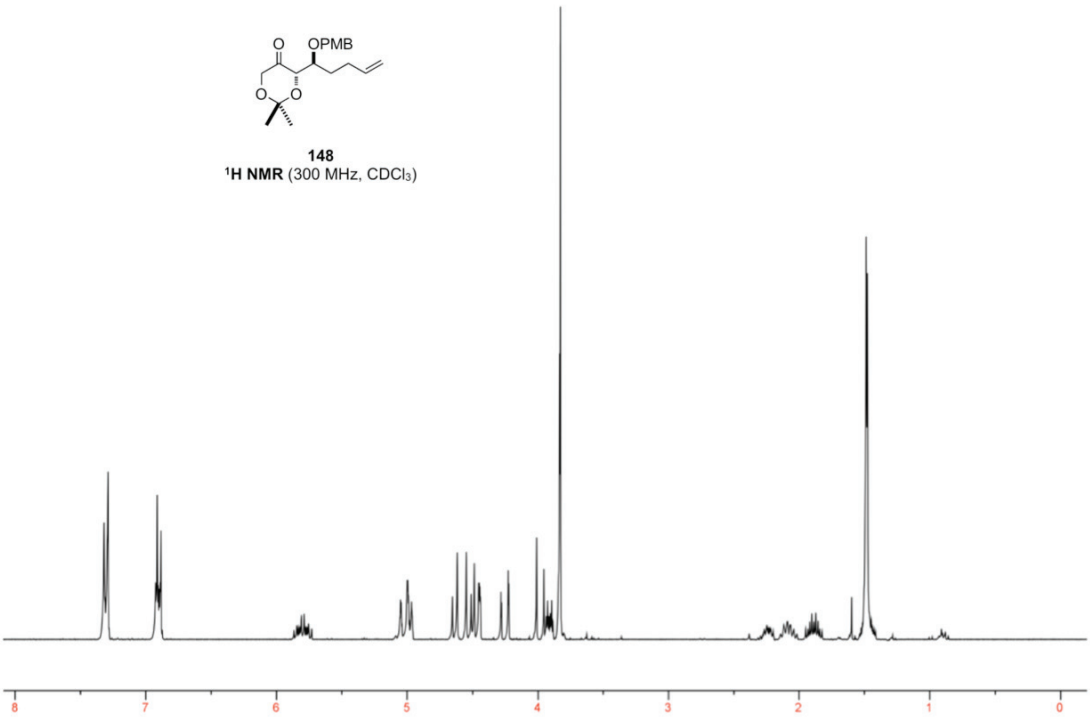
128
^{1}H NMR (300 MHz, $CDCl_3$)



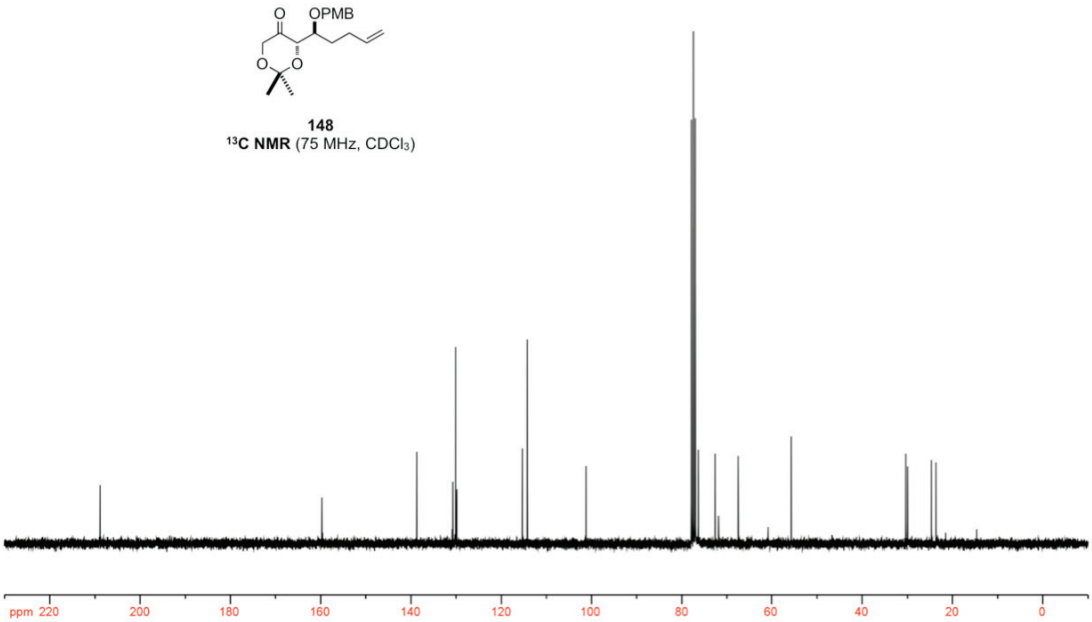


128
^{13}C NMR (75 MHz, $CDCl_3$)

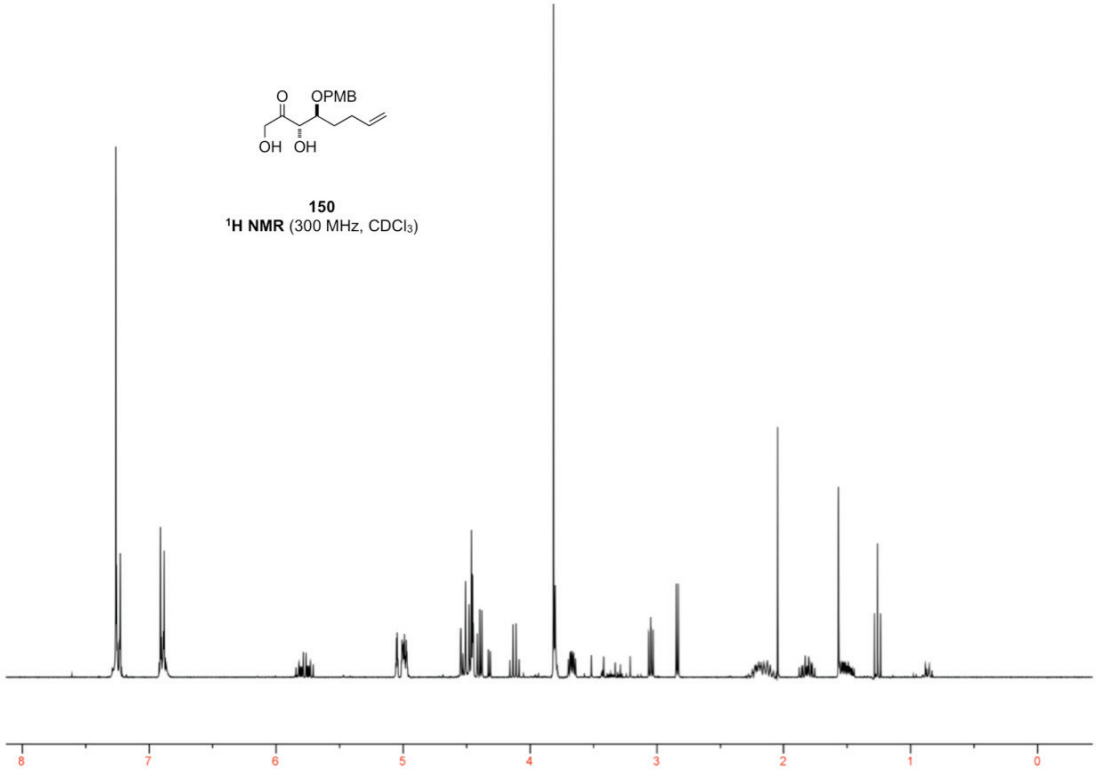




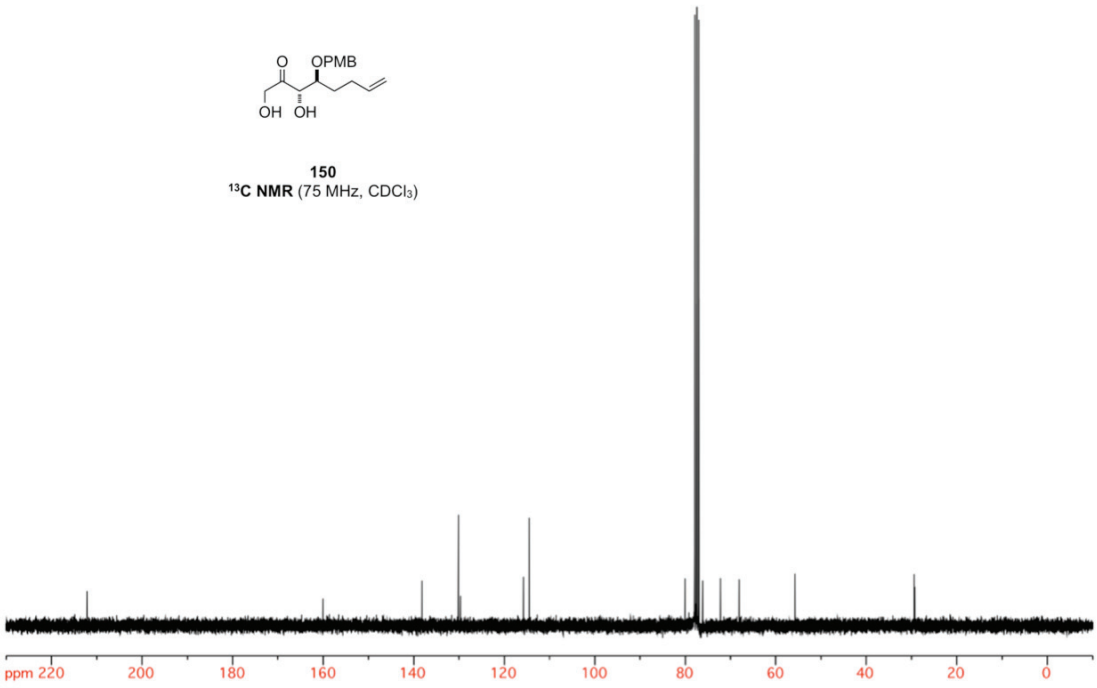
148
^{1}H NMR (300 MHz, $CDCl_3$)



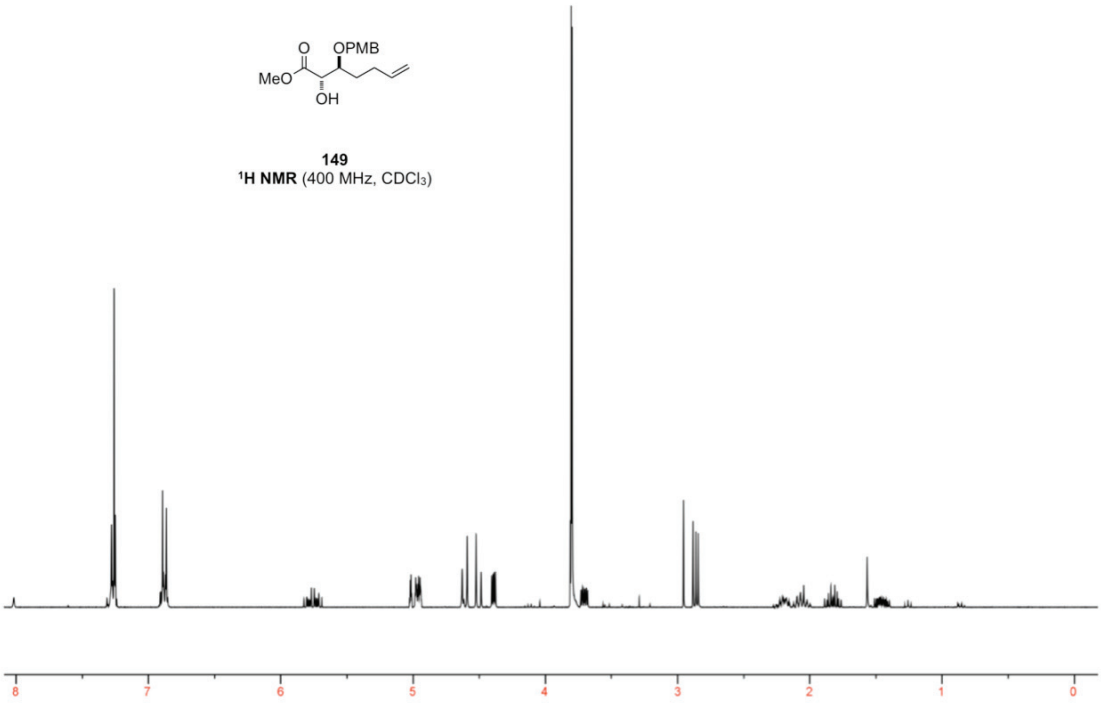
148
^{13}C NMR (75 MHz, $CDCl_3$)



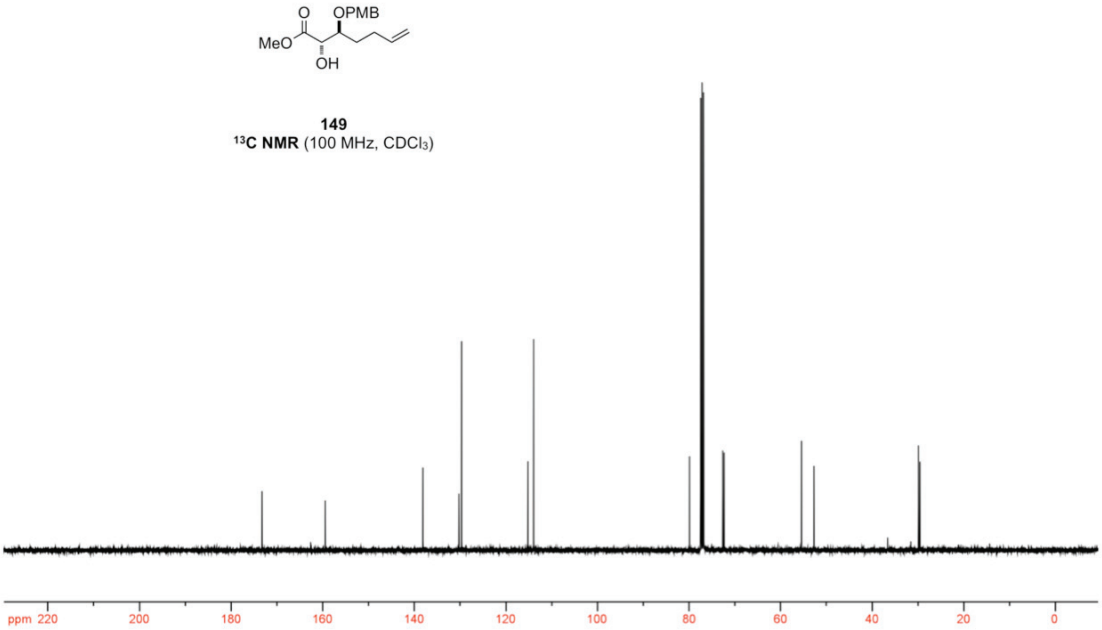
150
^{1}H NMR (300 MHz, $CDCl_3$)



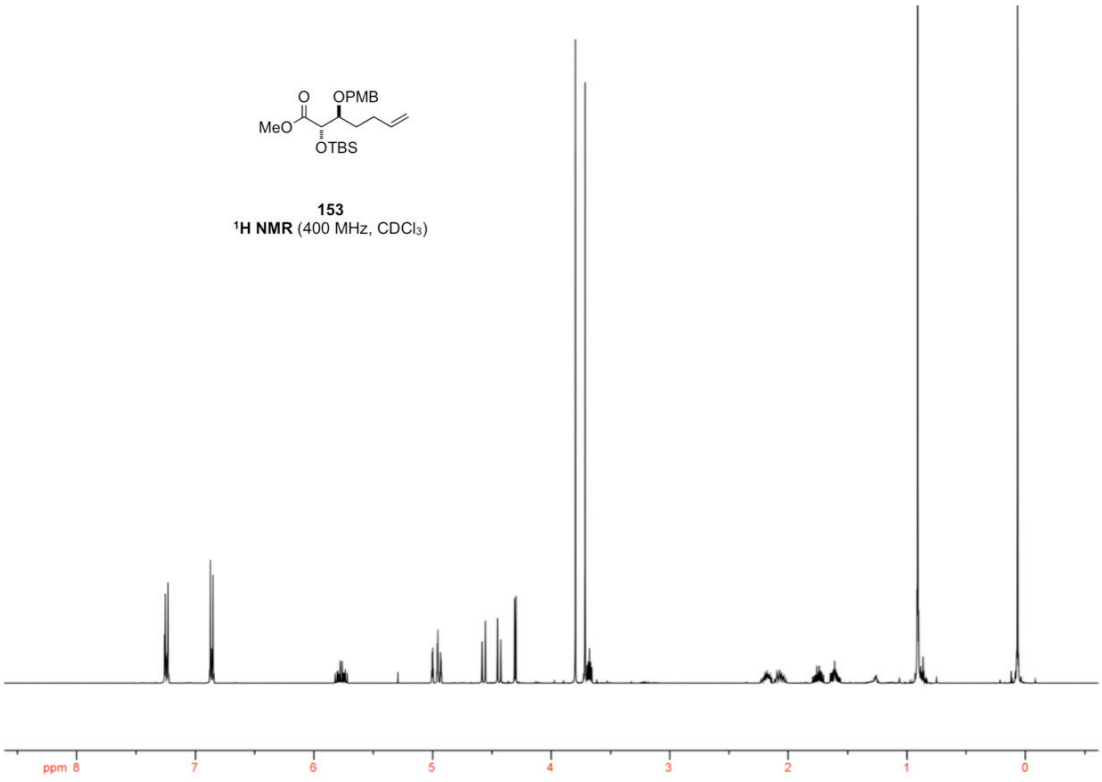
150
^{13}C NMR (75 MHz, $CDCl_3$)



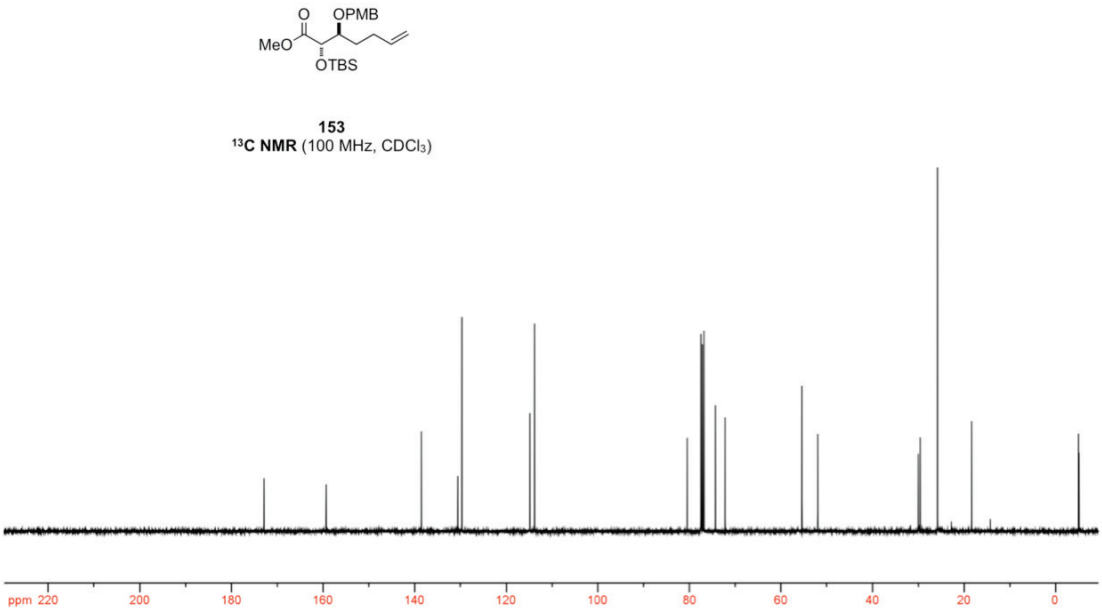
149
^{1}H NMR (400 MHz, $CDCl_3$)



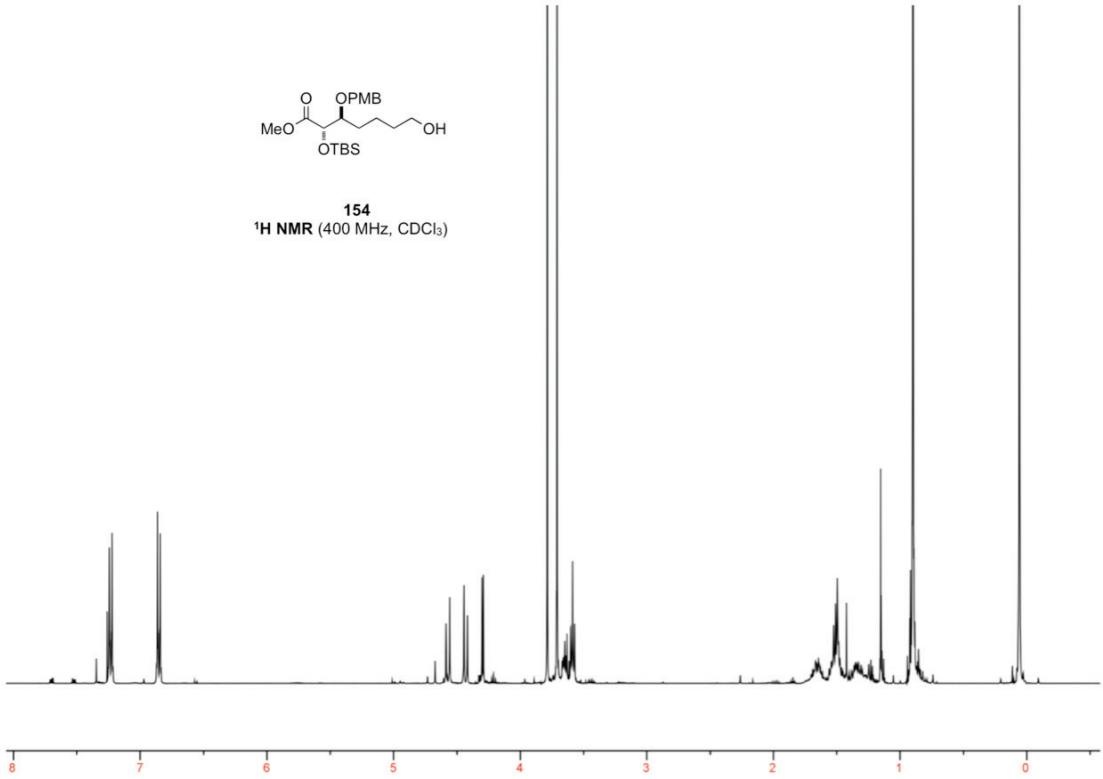
149
^{13}C NMR (100 MHz, $CDCl_3$)

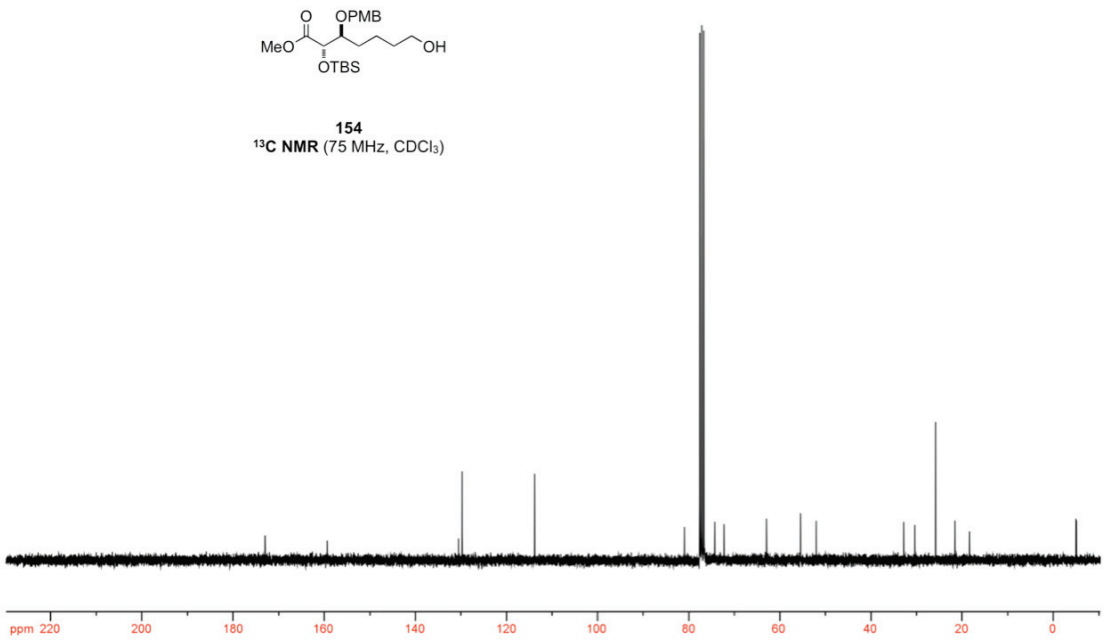


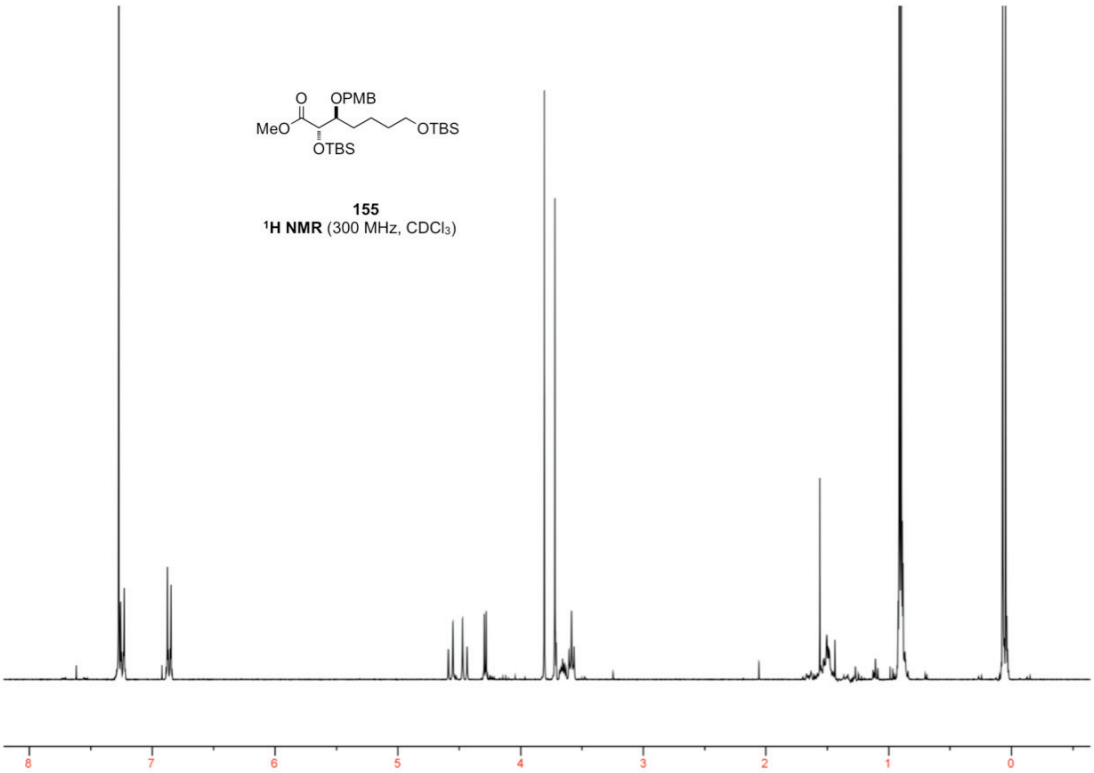
153
^{1}H NMR (400 MHz, $CDCl_3$)



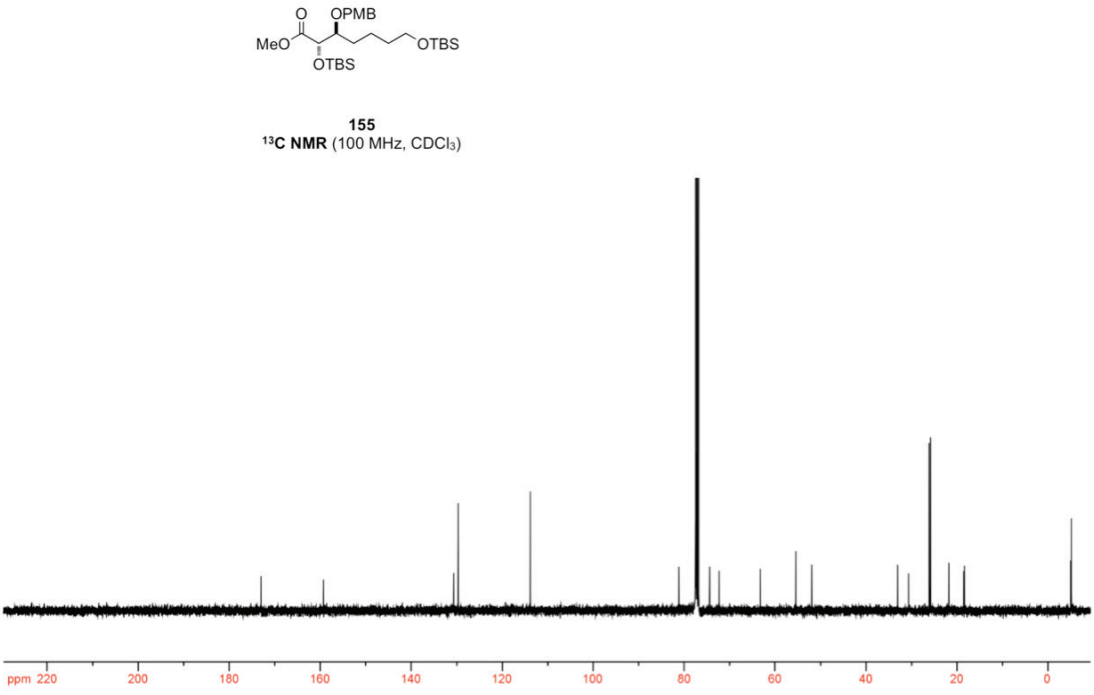
153
^{13}C NMR (100 MHz, $CDCl_3$)


O
OPMB
MeO
OH
OTBS
154
¹H NMR (400 MHz, CDCl₃)
8
7
6
5
4
3
2
1
0


O
OPMB
MeO
OH
OTBS
154
¹³C NMR (75 MHz, CDCl₃)
ppm 220
200
180
160
140
120
100
80
60
40
20
0

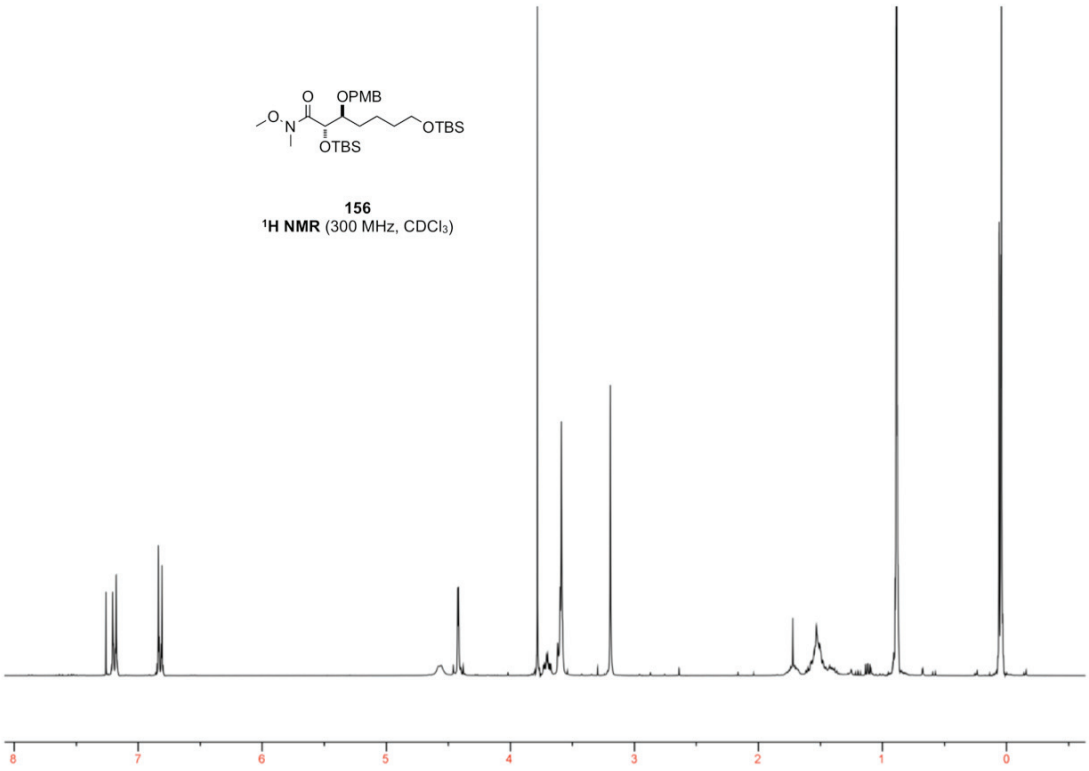


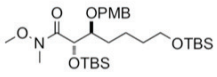
155
^{1}H NMR (300 MHz, $CDCl_3$)



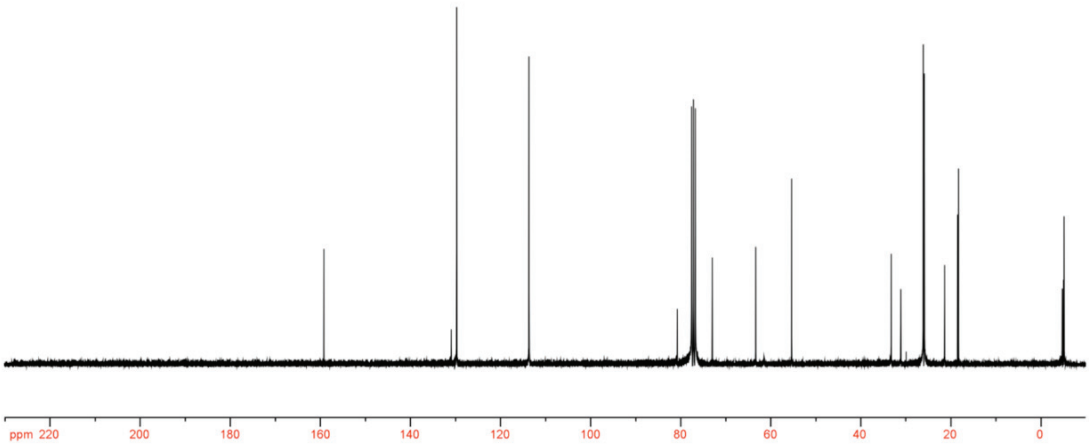
155
^{13}C NMR (100 MHz, $CDCl_3$)

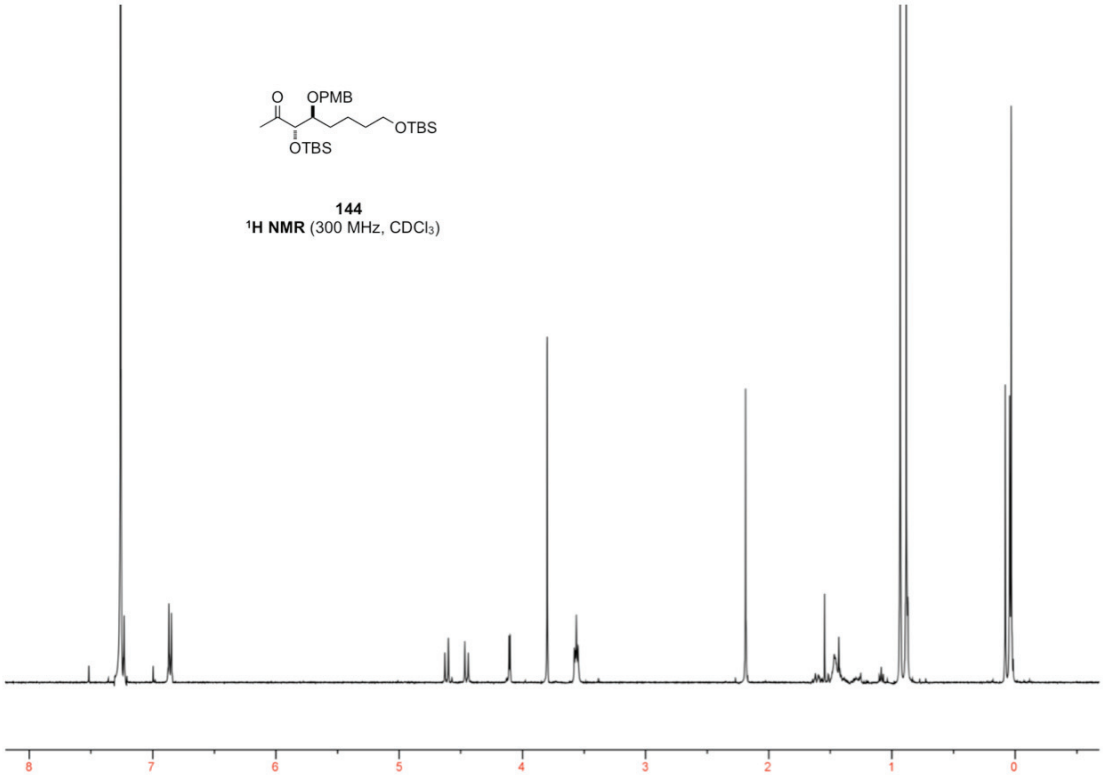
156
^{1}H NMR (300 MHz, $CDCl_3$)

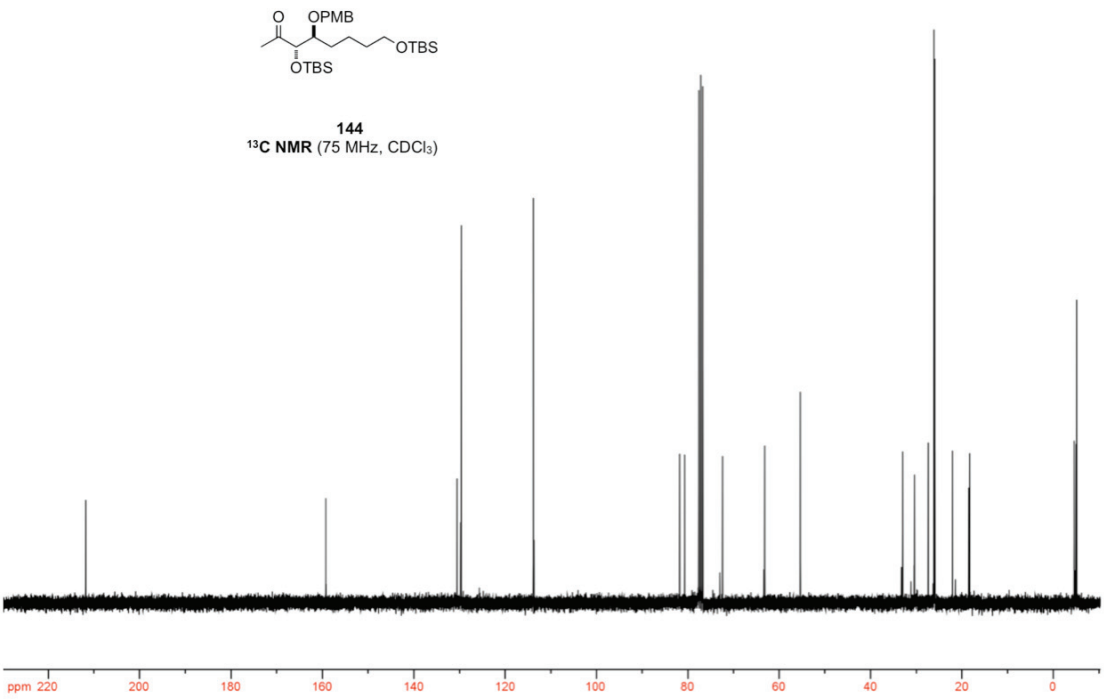


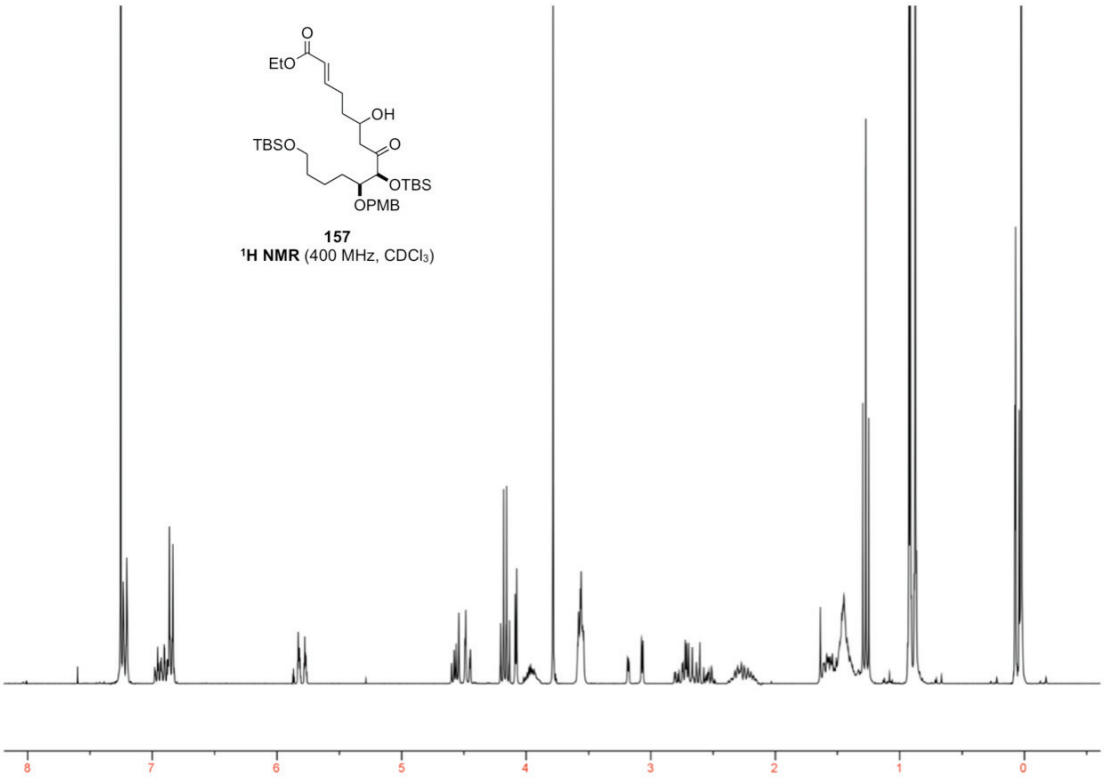


156
^{13}C NMR (75 MHz, $CDCl_3$)

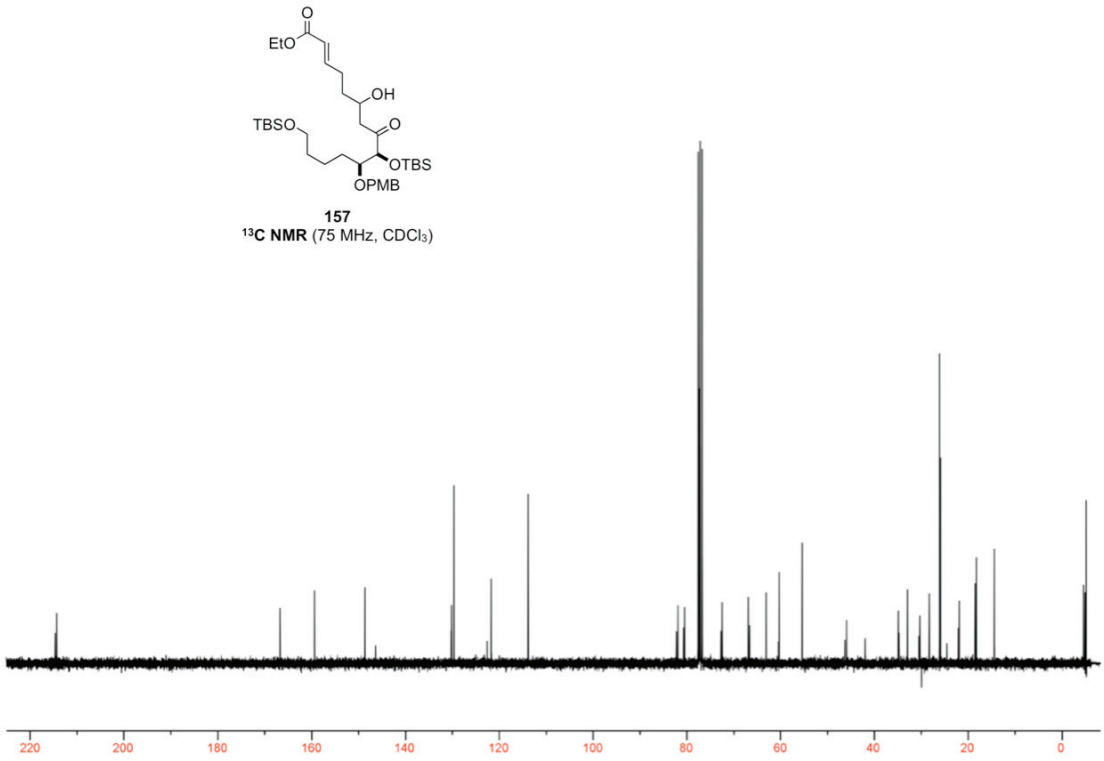



O
OPMB
OTBS
OTBS
144
¹H NMR (300 MHz, CDCl₃)
8
7
6
5
4
3
2
1
0

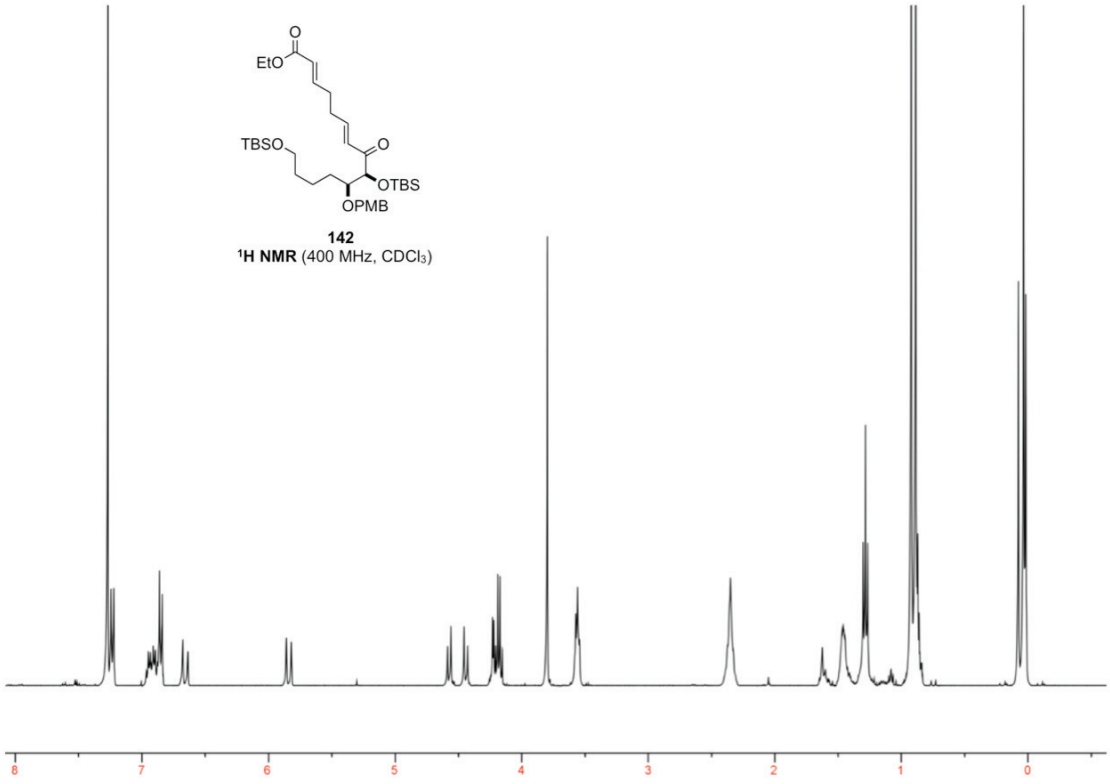

O
OPMB
OTBS
OTBS
144
¹³C NMR (75 MHz, CDCl₃)
ppm 220
200
180
160
140
120
100
80
60
40
20
0



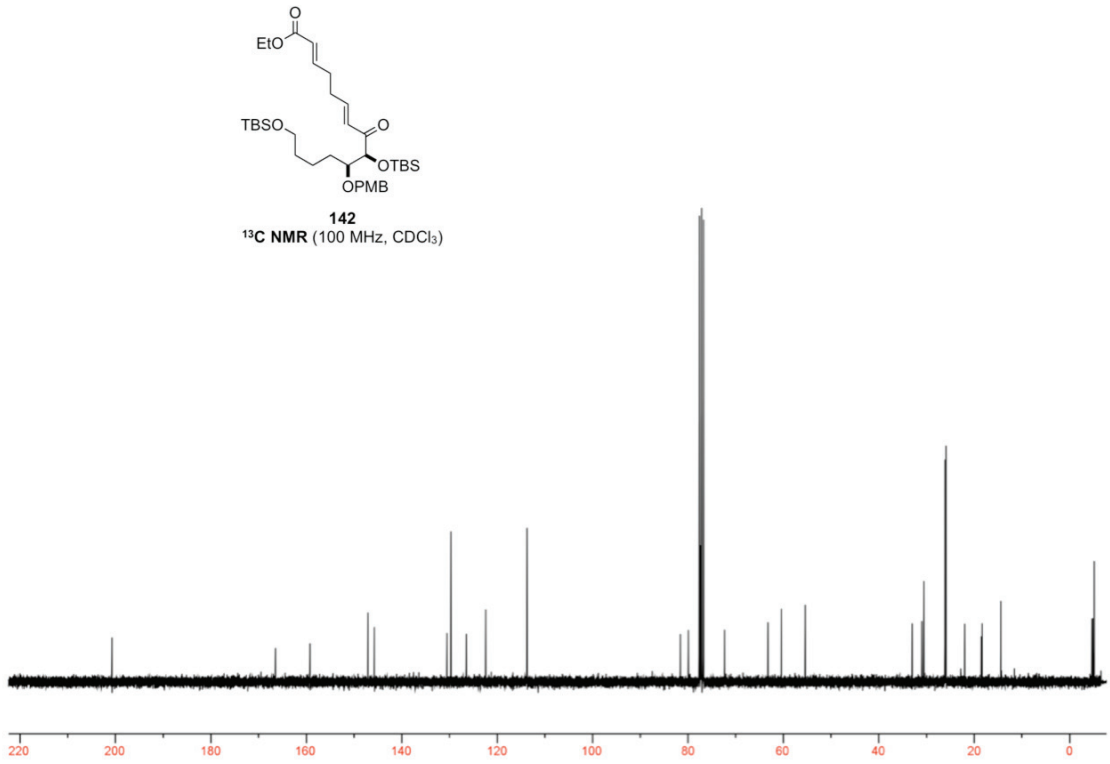
157
^{1}H NMR (400 MHz, $CDCl_3$)



157
^{13}C NMR (75 MHz, $CDCl_3$)

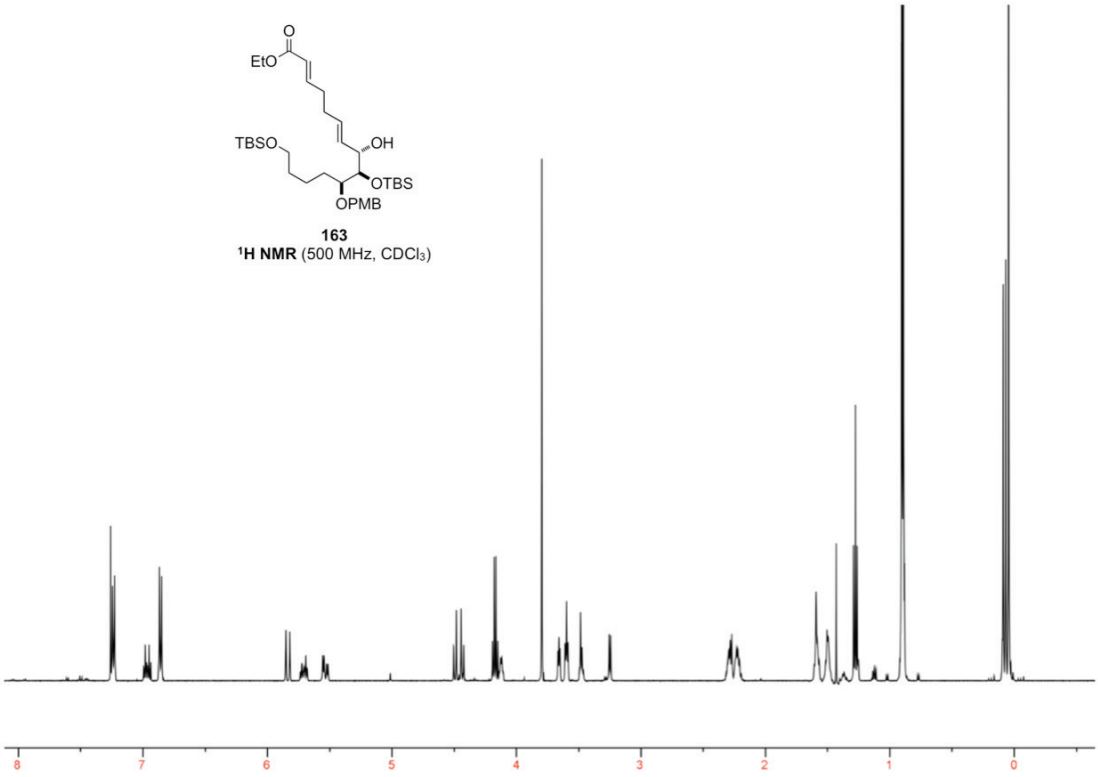


142
^{1}H NMR (400 MHz, $CDCl_3$)

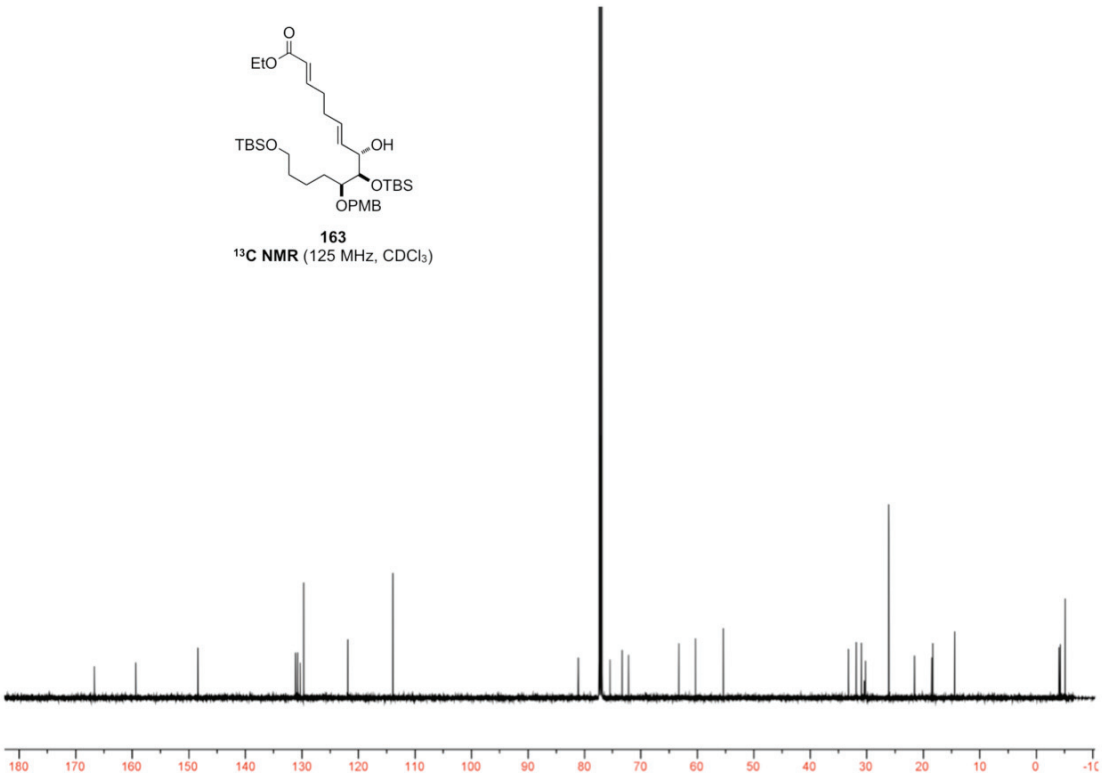


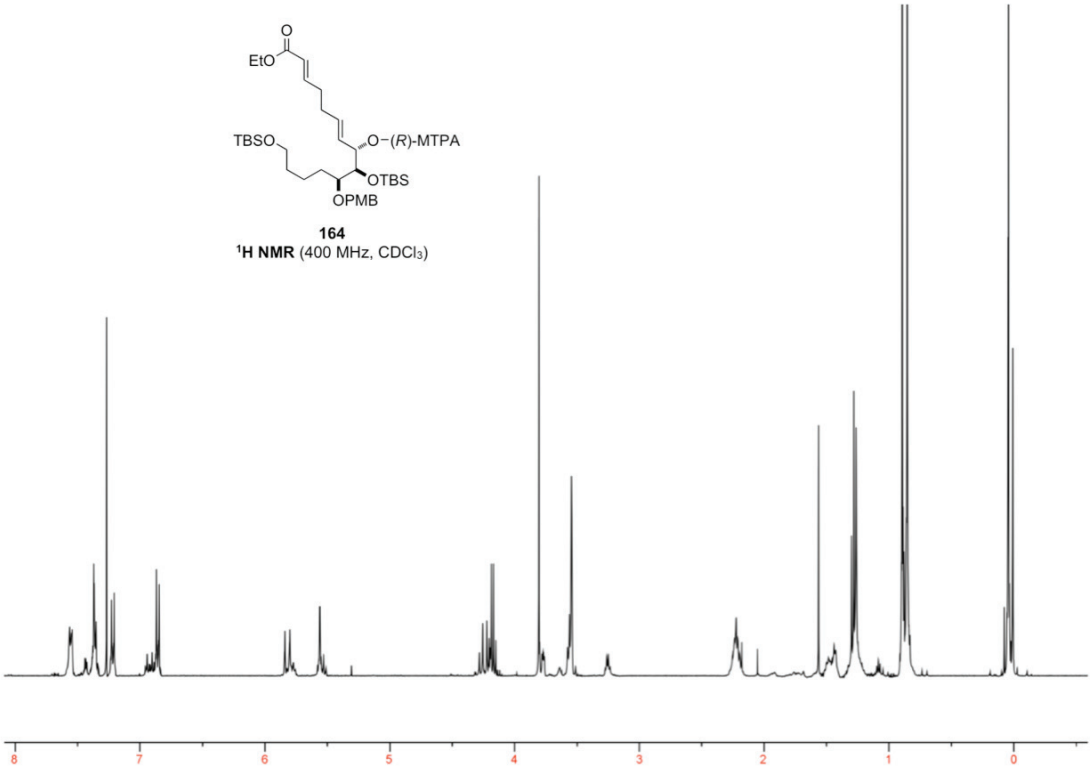
142
^{13}C NMR (100 MHz, $CDCl_3$)

163
^{1}H NMR (500 MHz, $CDCl_3$)

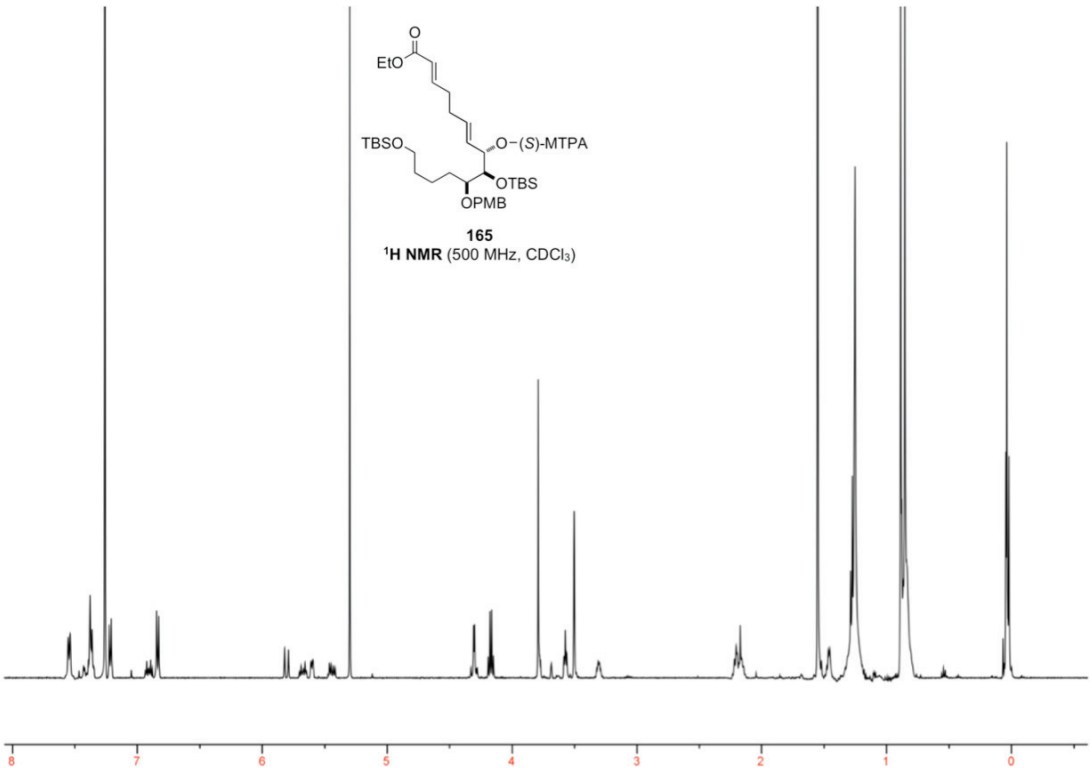


163
^{13}C NMR (125 MHz, $CDCl_3$)

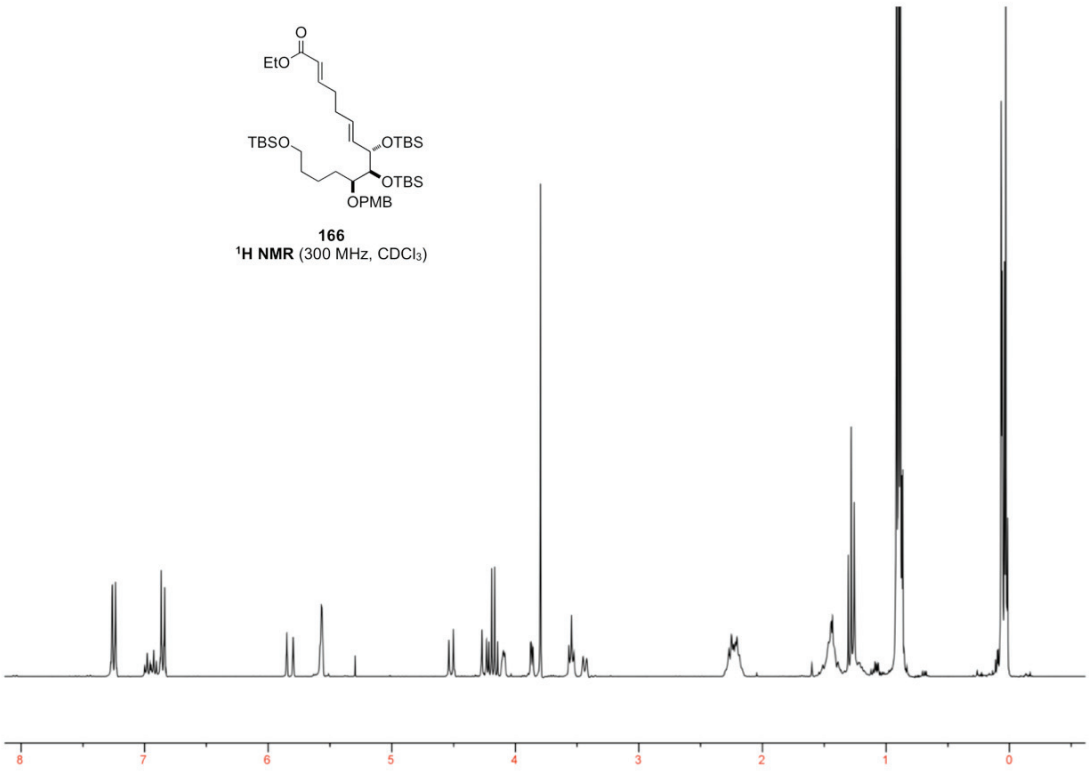




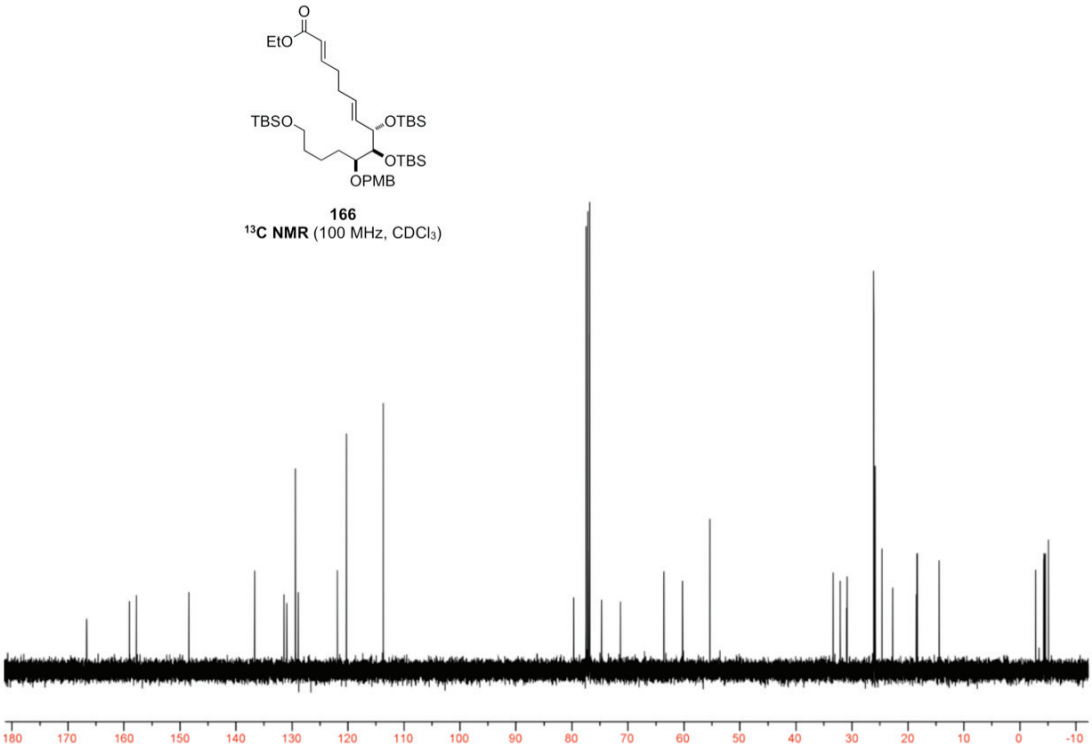
164
^{1}H NMR (400 MHz, $CDCl_3$)



165
^{1}H NMR (500 MHz, $CDCl_3$)

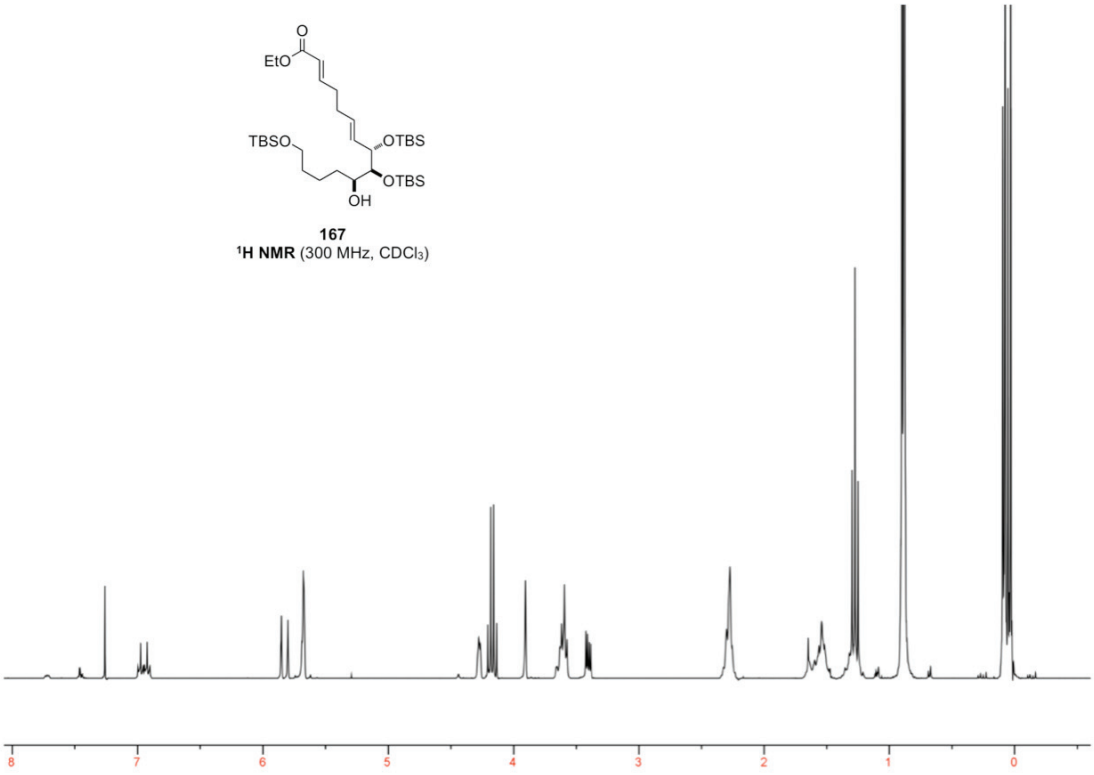


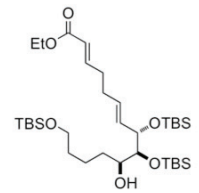
166
^{1}H NMR (300 MHz, $CDCl_3$)



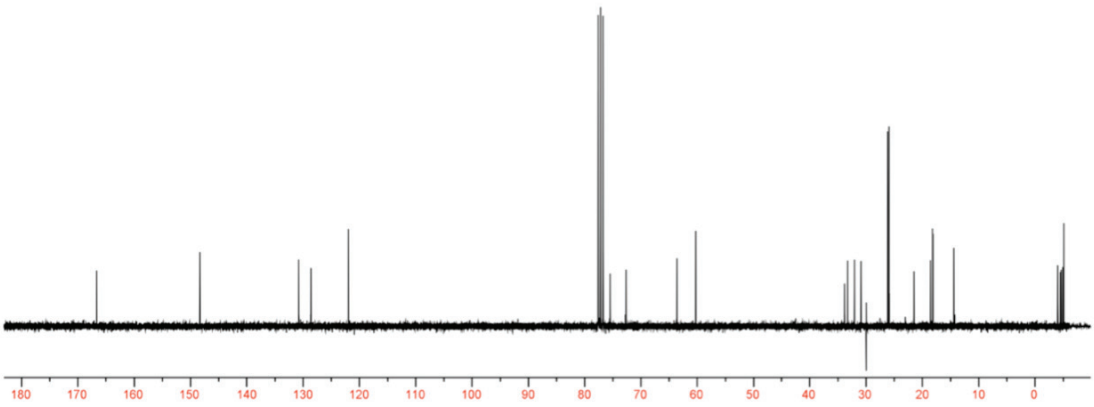
166
^{13}C NMR (100 MHz, $CDCl_3$)

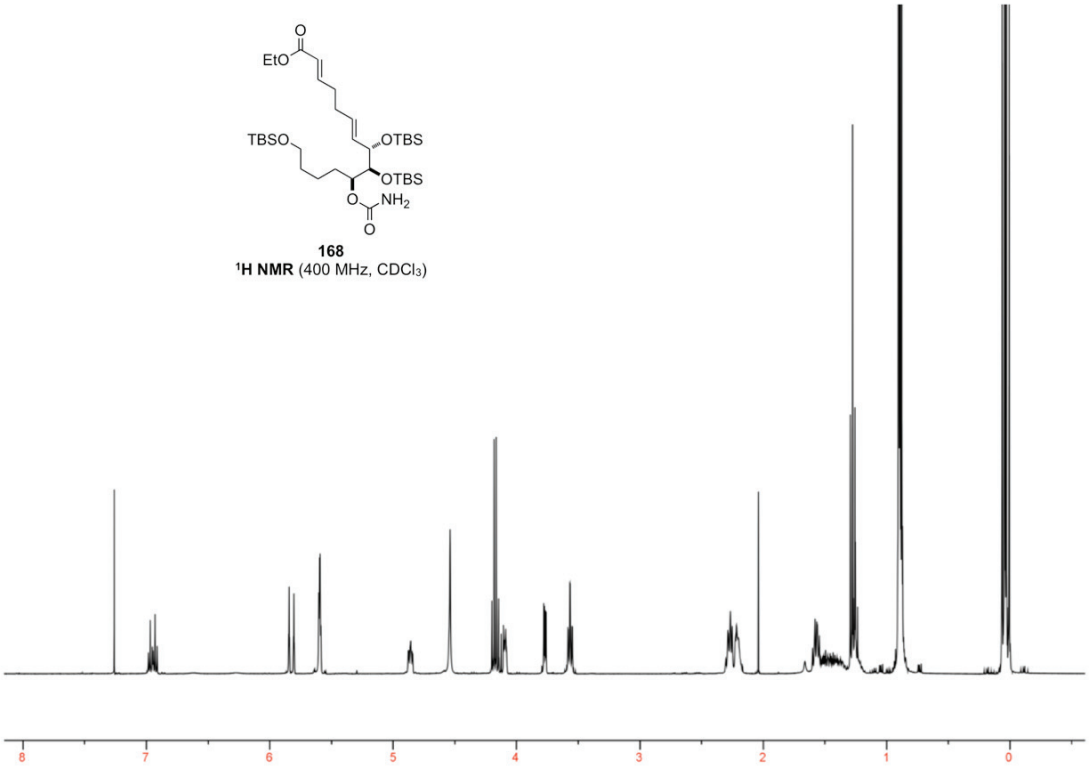
167
^{1}H NMR (300 MHz, $CDCl_3$)



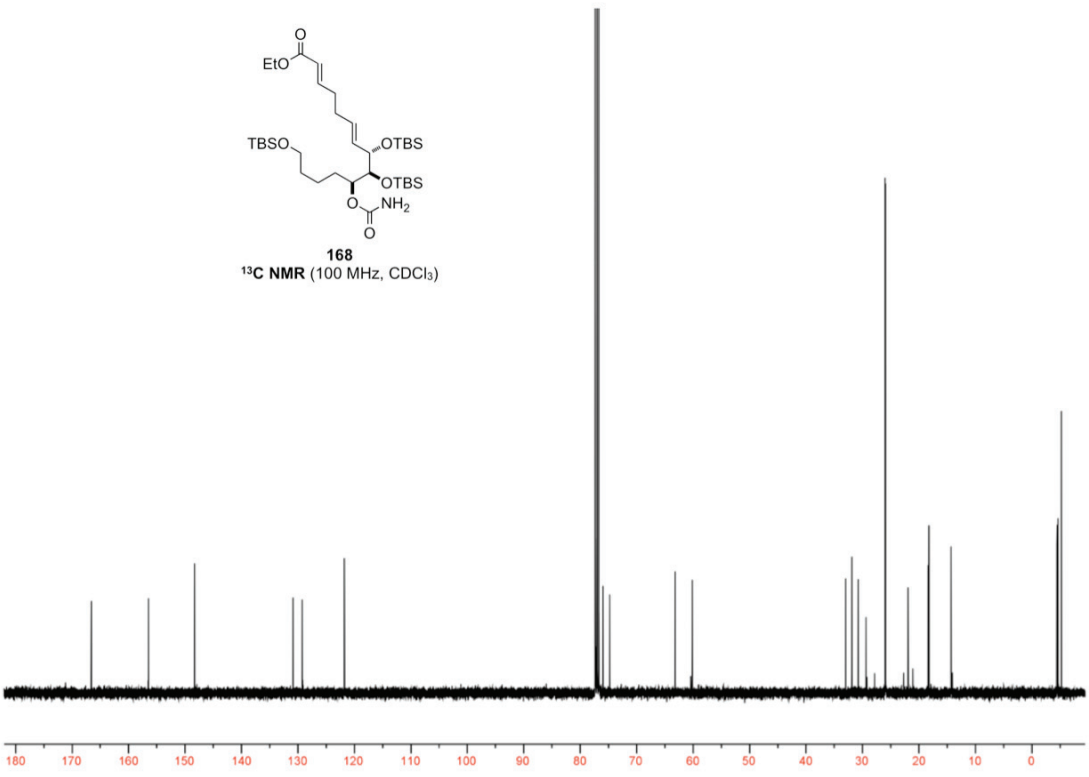


167
^{13}C NMR (75 MHz, $CDCl_3$)

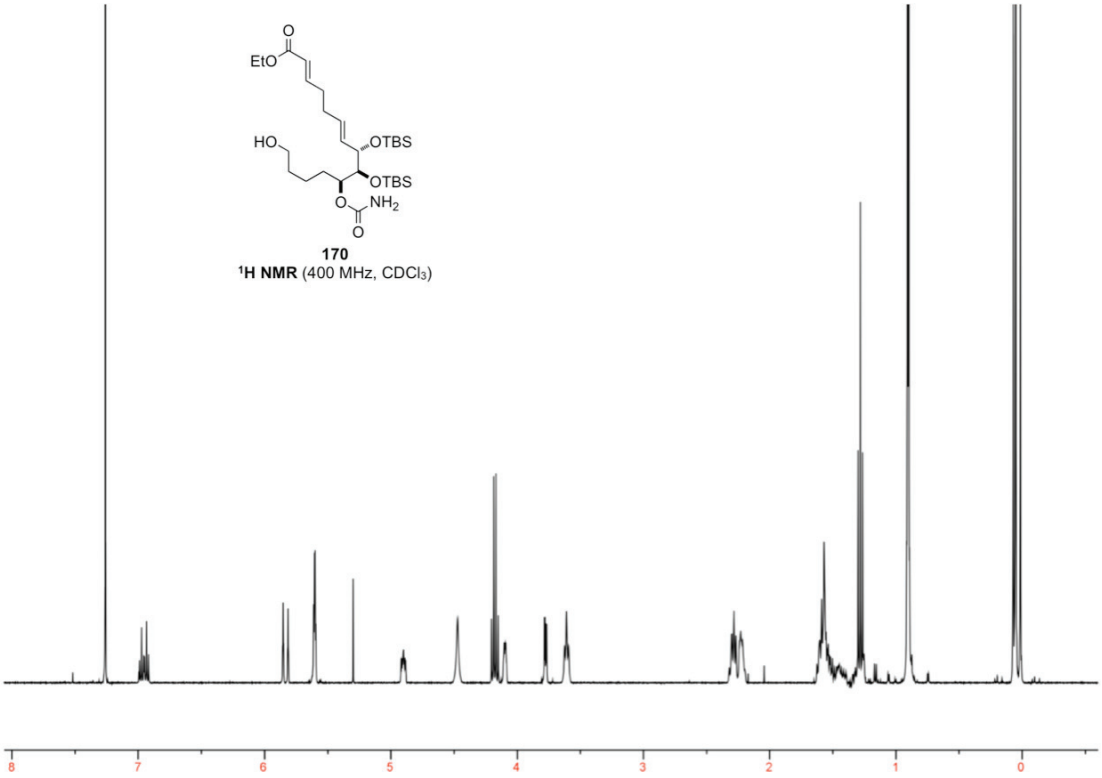




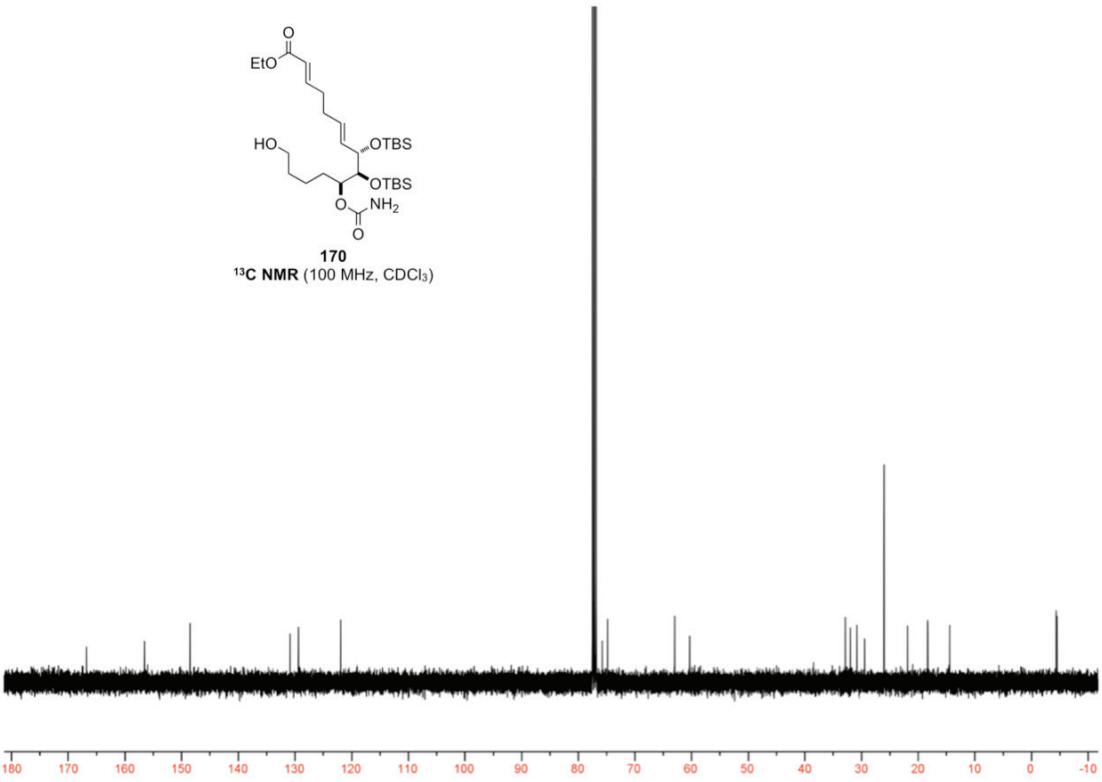
168
^{1}H NMR (400 MHz, $CDCl_3$)



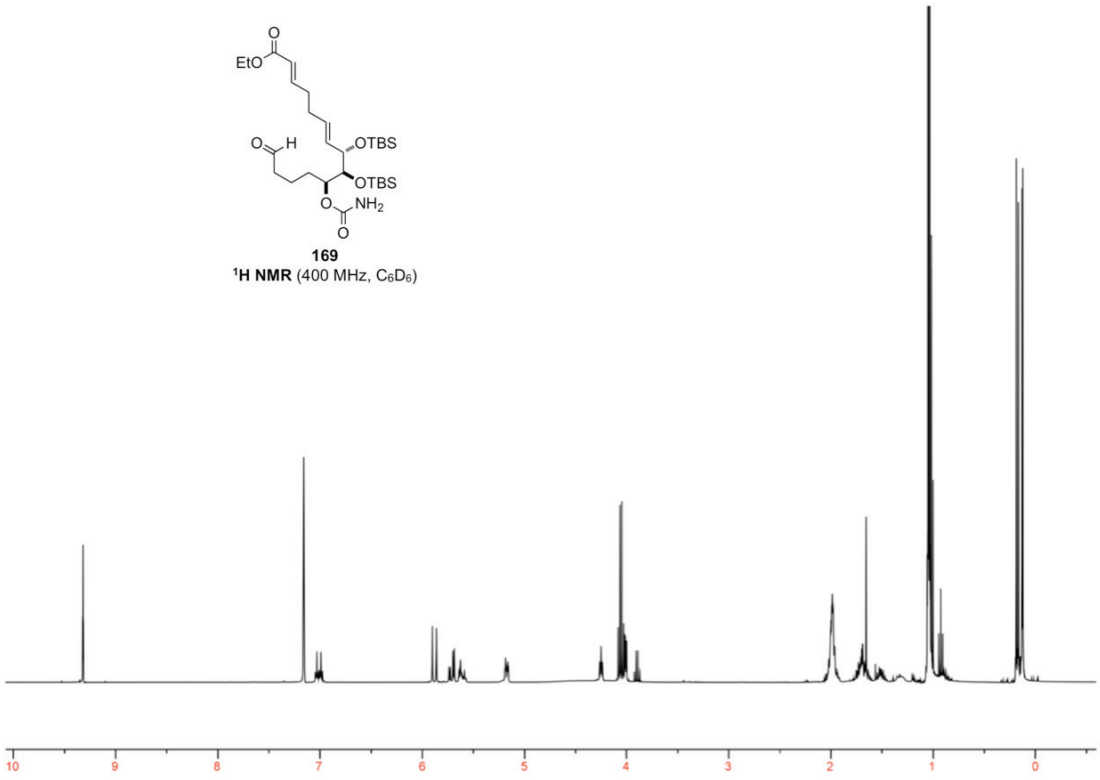
168
^{13}C NMR (100 MHz, $CDCl_3$)



170
^{1}H NMR (400 MHz, $CDCl_3$)

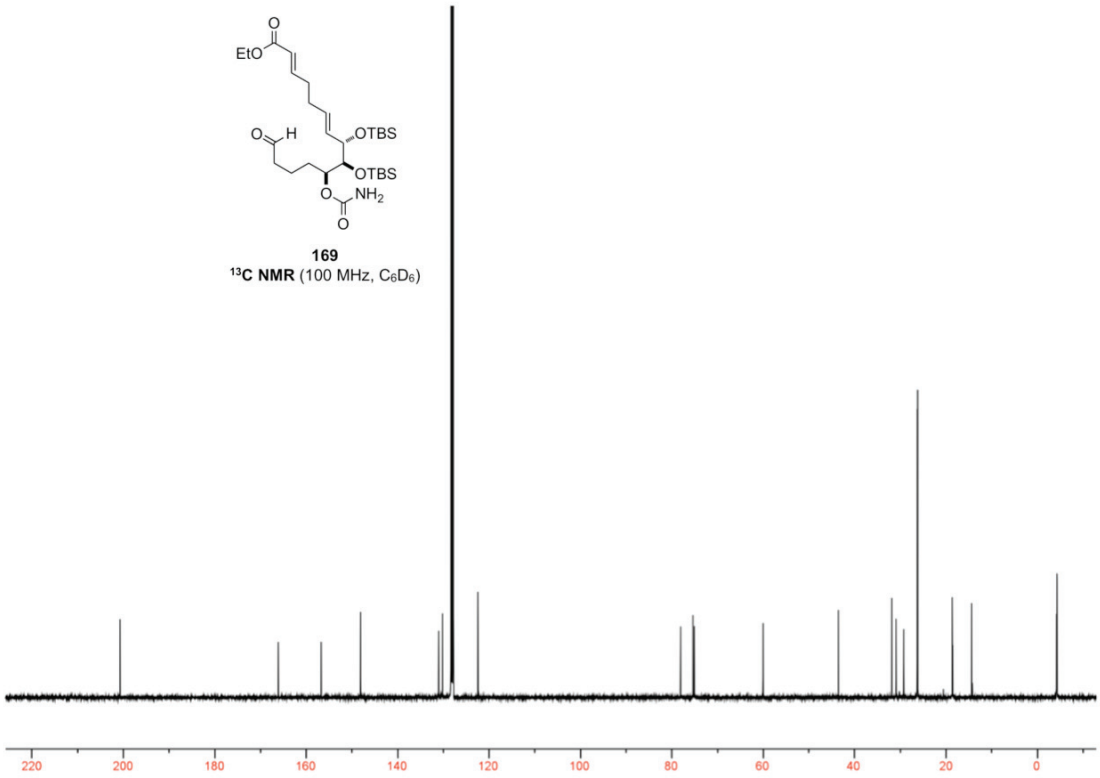


170
^{13}C NMR (100 MHz, $CDCl_3$)



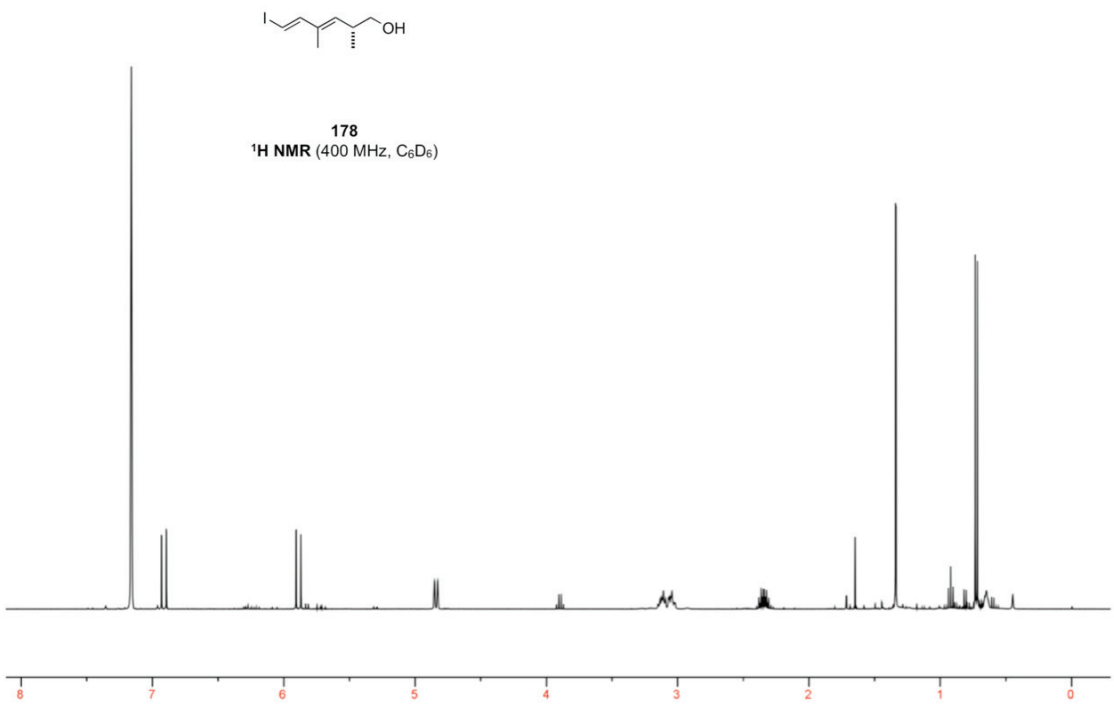
169

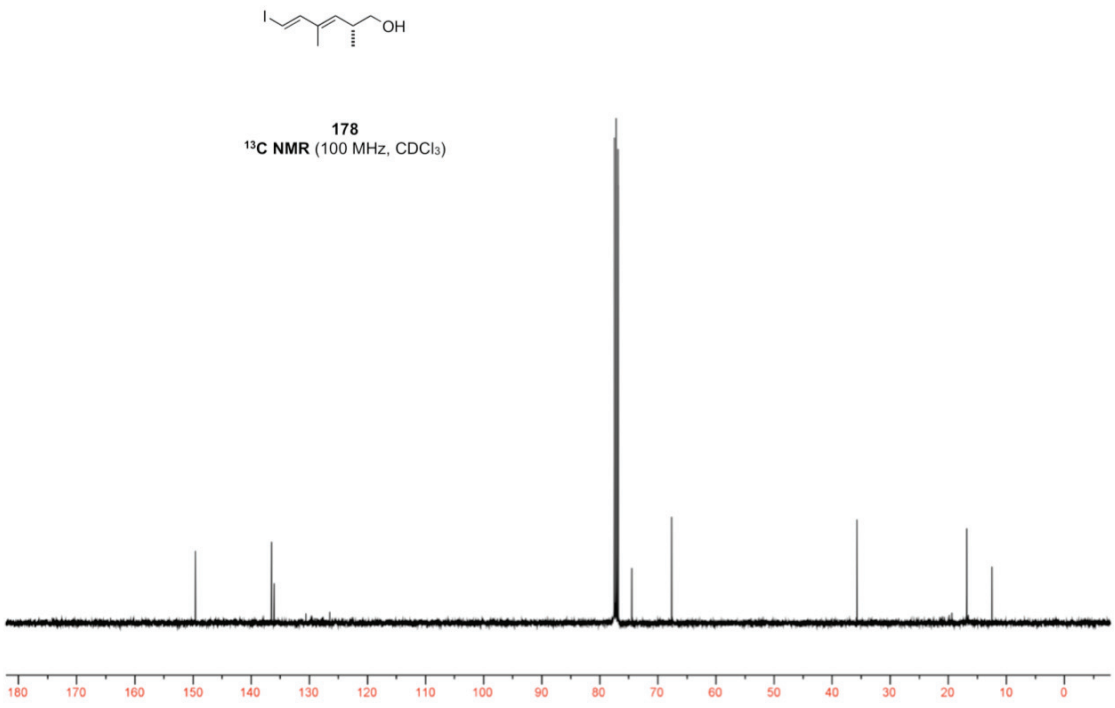
^{1}H NMR (400 MHz, C_6D_6)

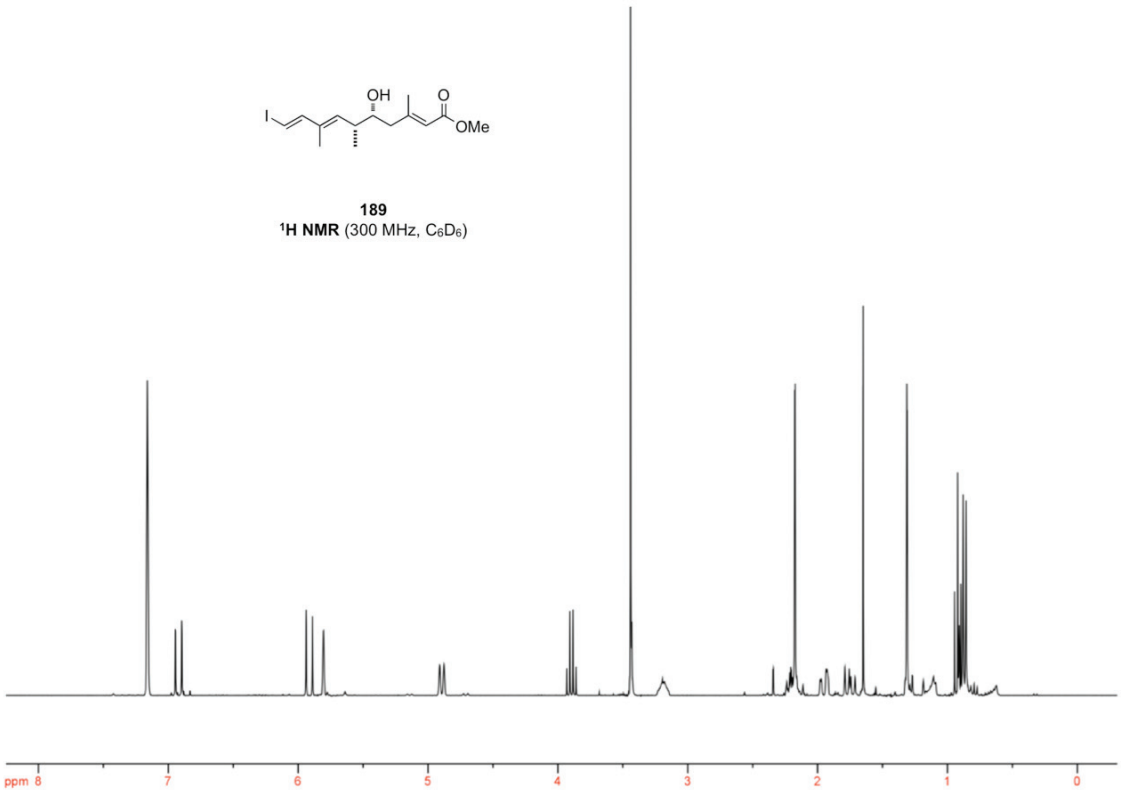


169

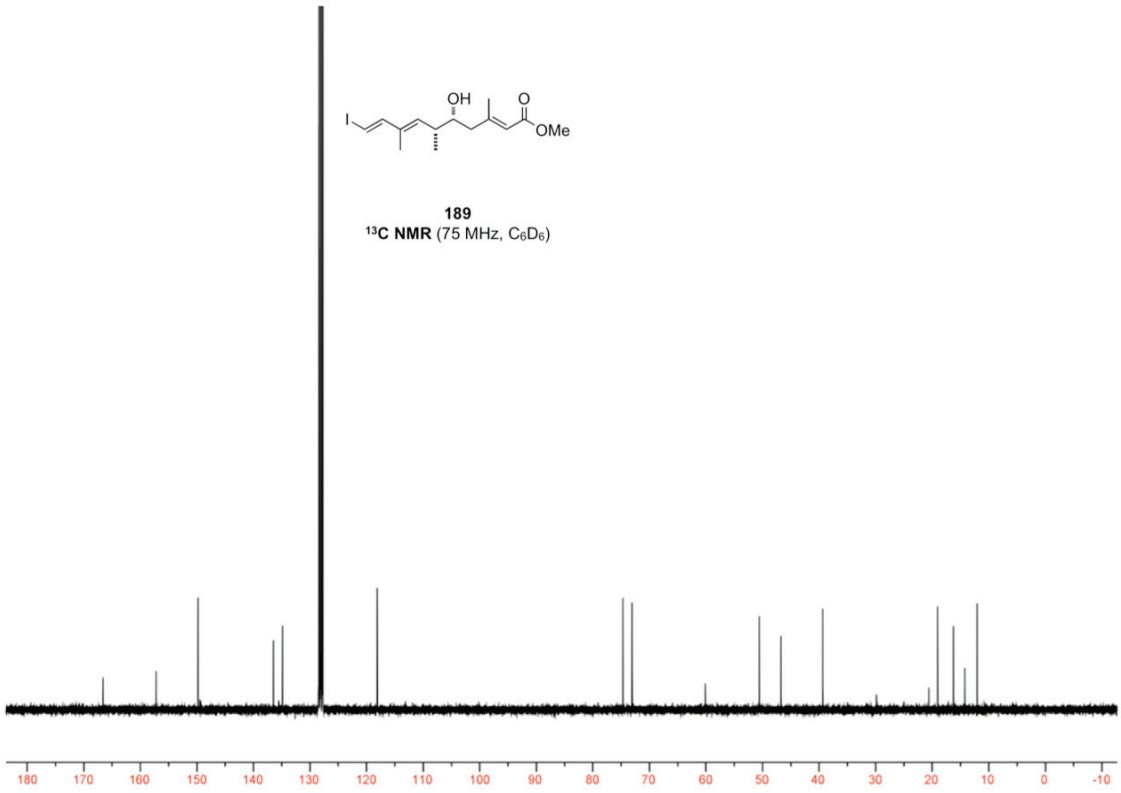
^{13}C NMR (100 MHz, C_6D_6)


I
OH
178
¹H NMR (400 MHz, C6D6)
8
7
6
5
4
3
2
1
0


I
OH
178
¹³C NMR (100 MHz, CDCl3)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

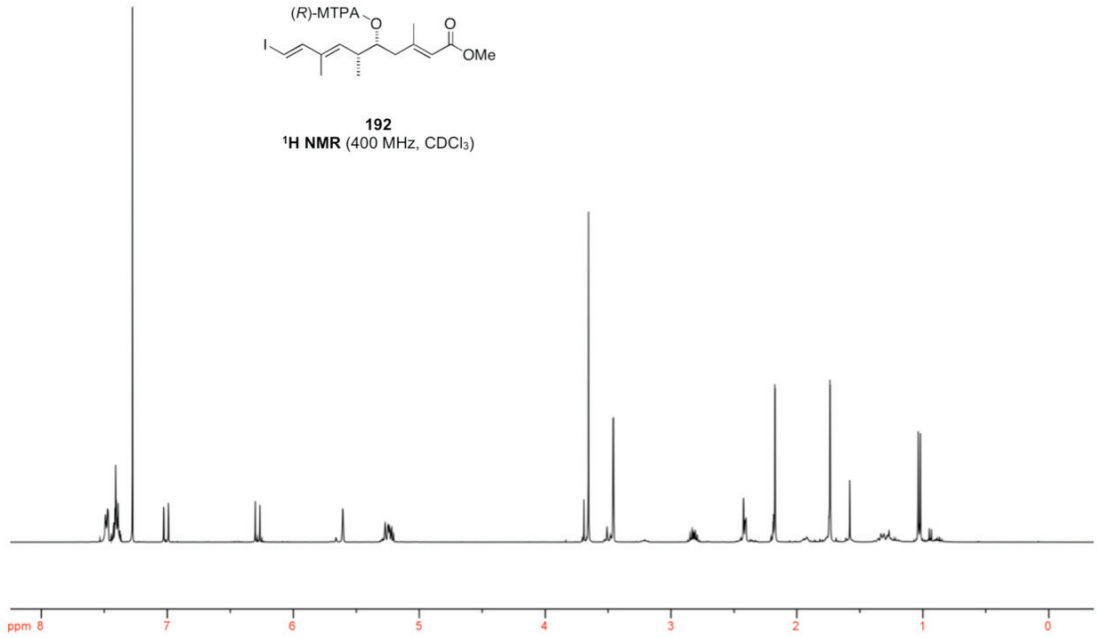


189
^{1}H NMR (300 MHz, C_6D_6)

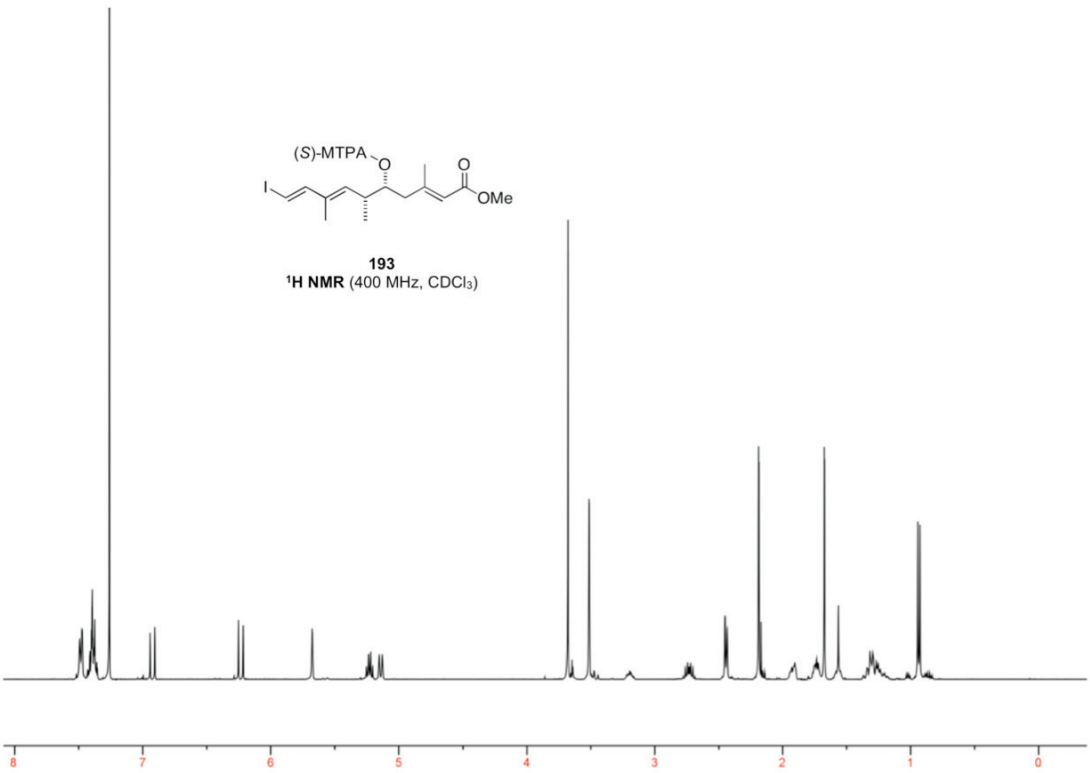


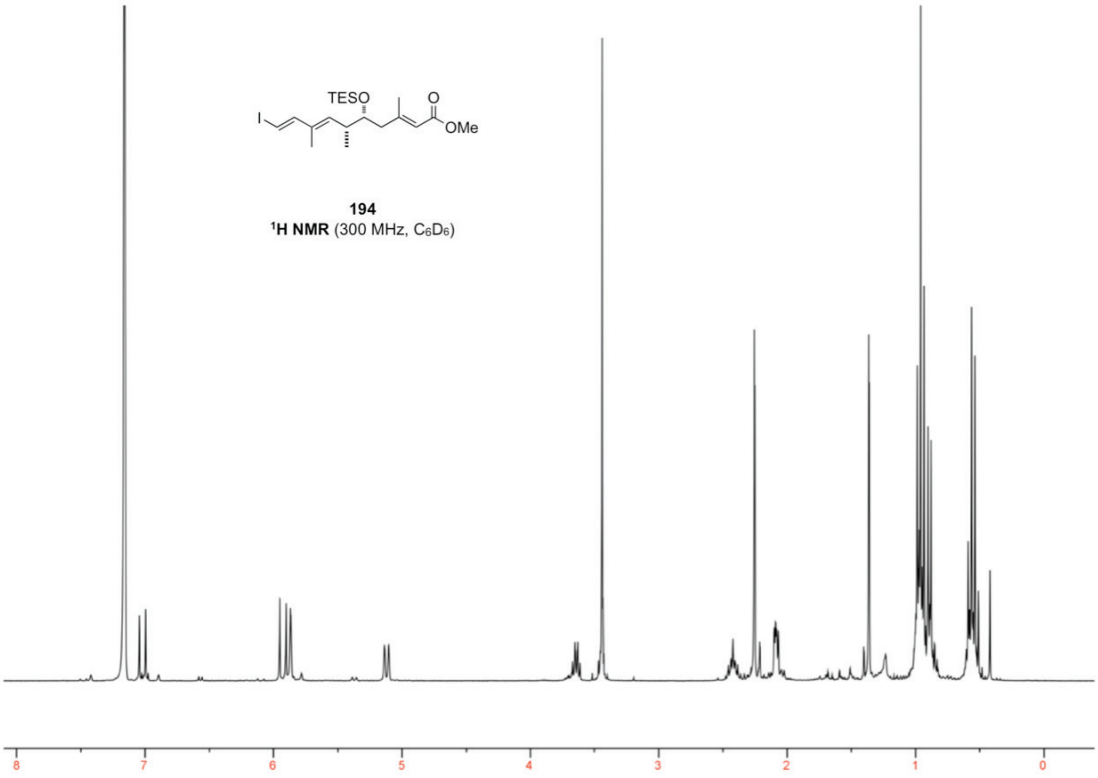
189
^{13}C NMR (75 MHz, C_6D_6)

192
^{1}H NMR (400 MHz, $CDCl_3$)

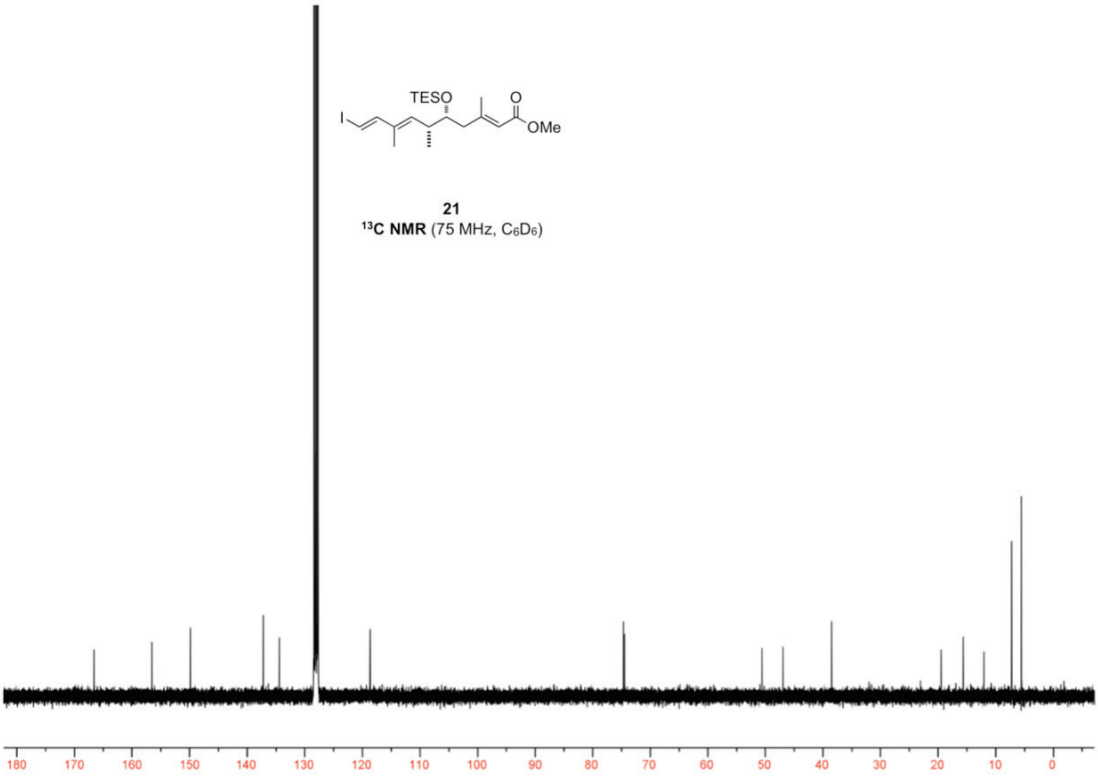


193
^{1}H NMR (400 MHz, $CDCl_3$)

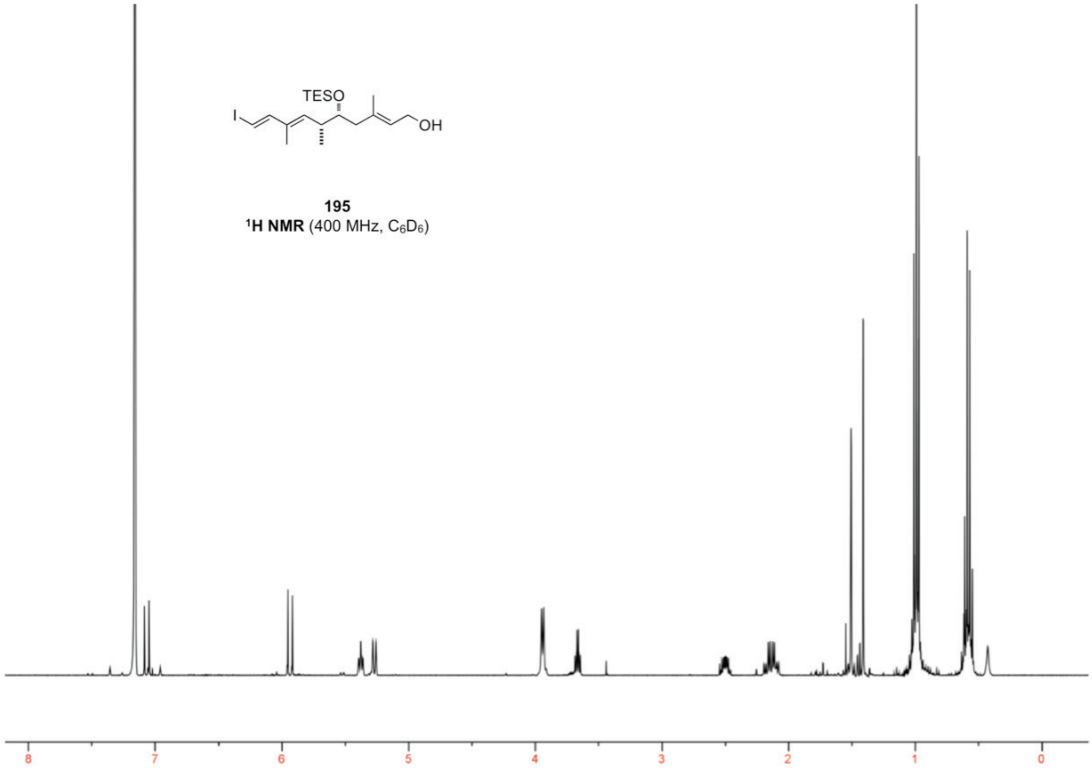


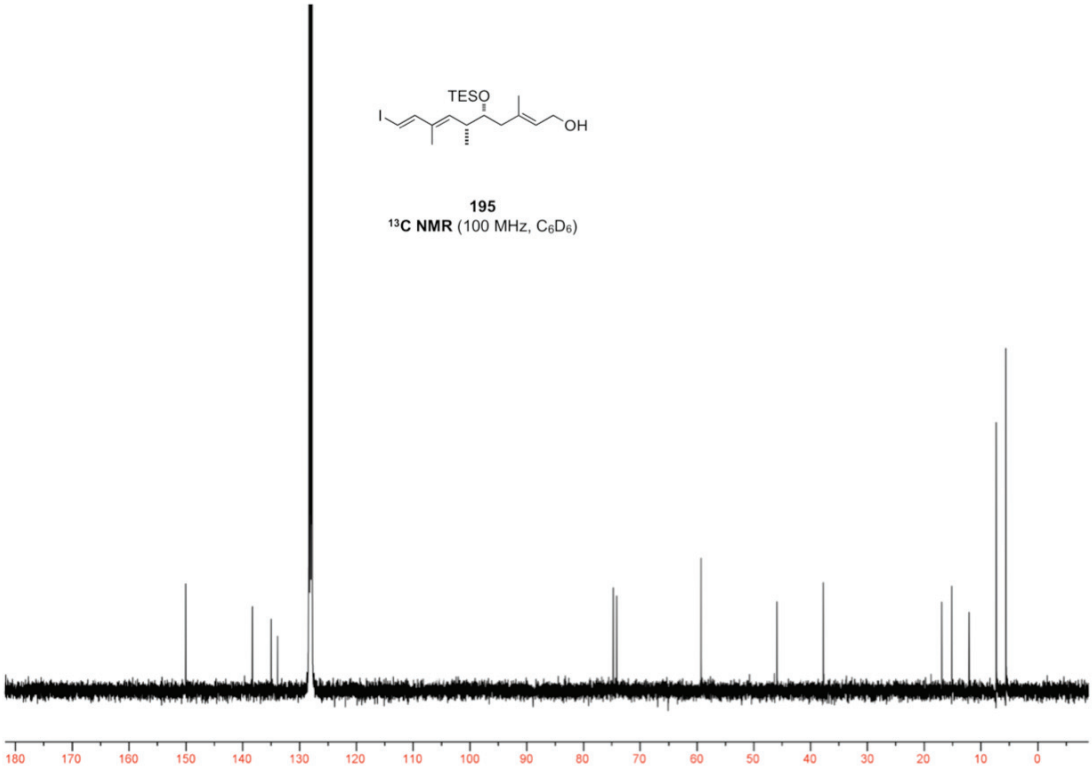


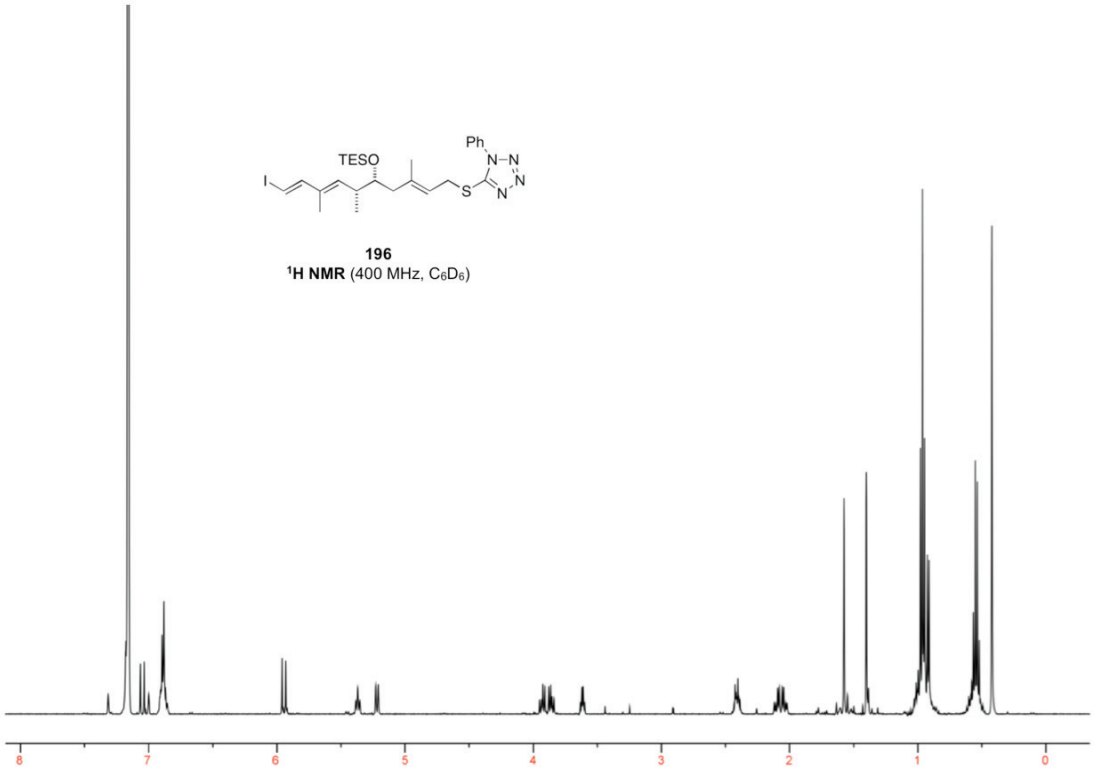
194
^{1}H NMR (300 MHz, C_6D_6)



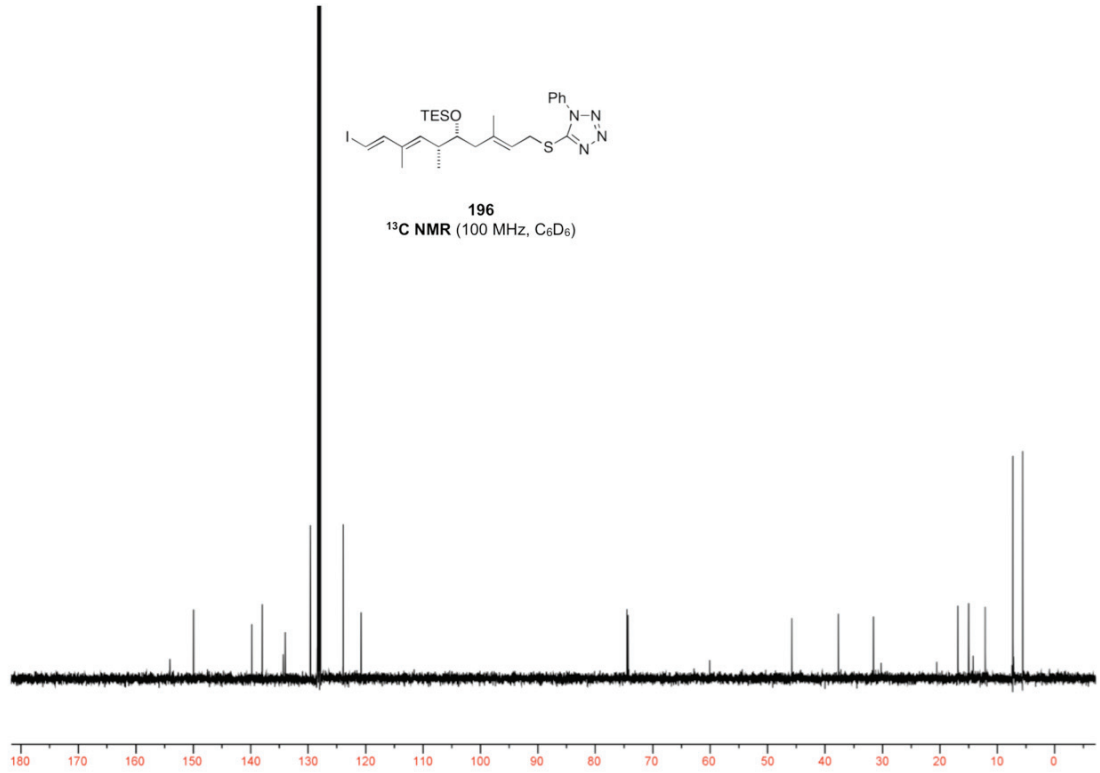
21
^{13}C NMR (75 MHz, C_6D_6)


TESO
I
OH
195
¹H NMR (400 MHz, C6D6)
8
7
6
5
4
3
2
1
0

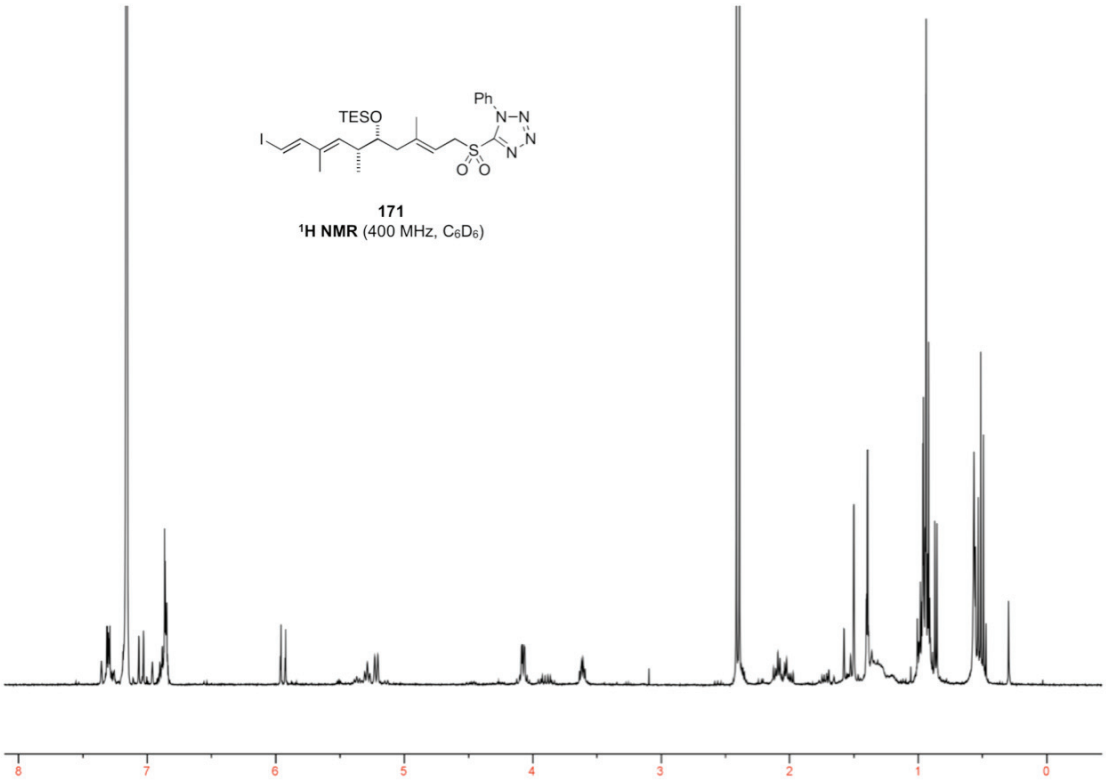

TESO
I
OH
195
¹³C NMR (100 MHz, C6D6)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0



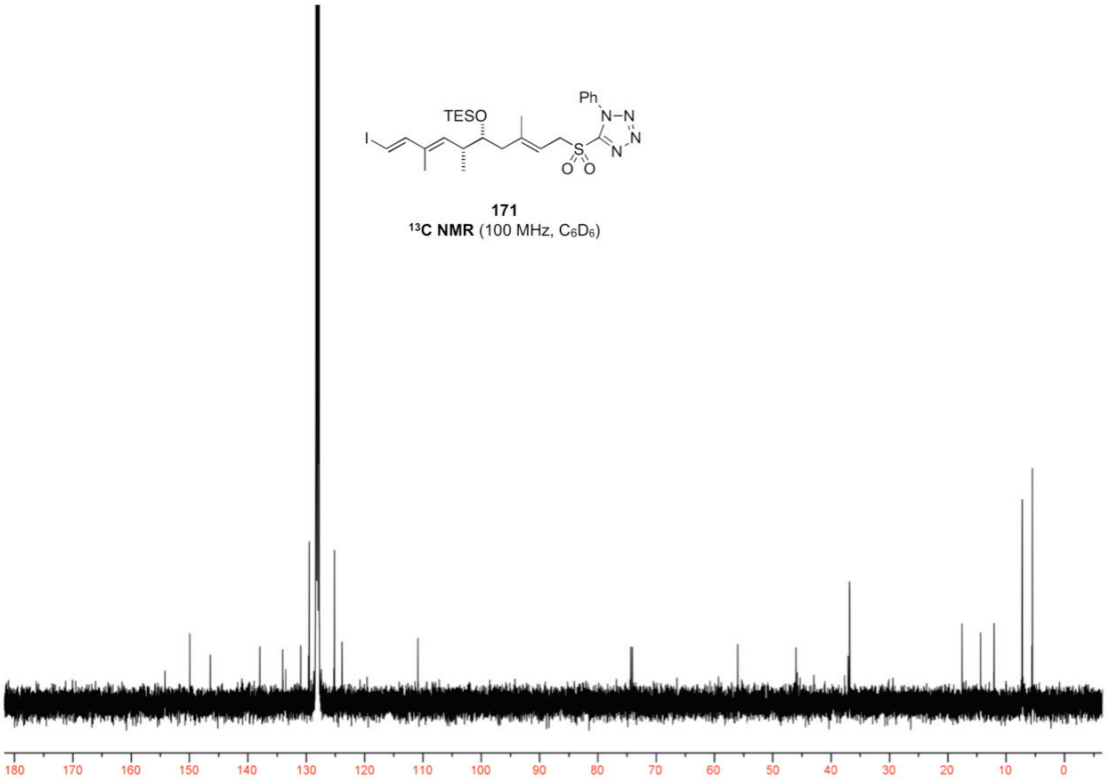
196
^{1}H NMR (400 MHz, C_6D_6)



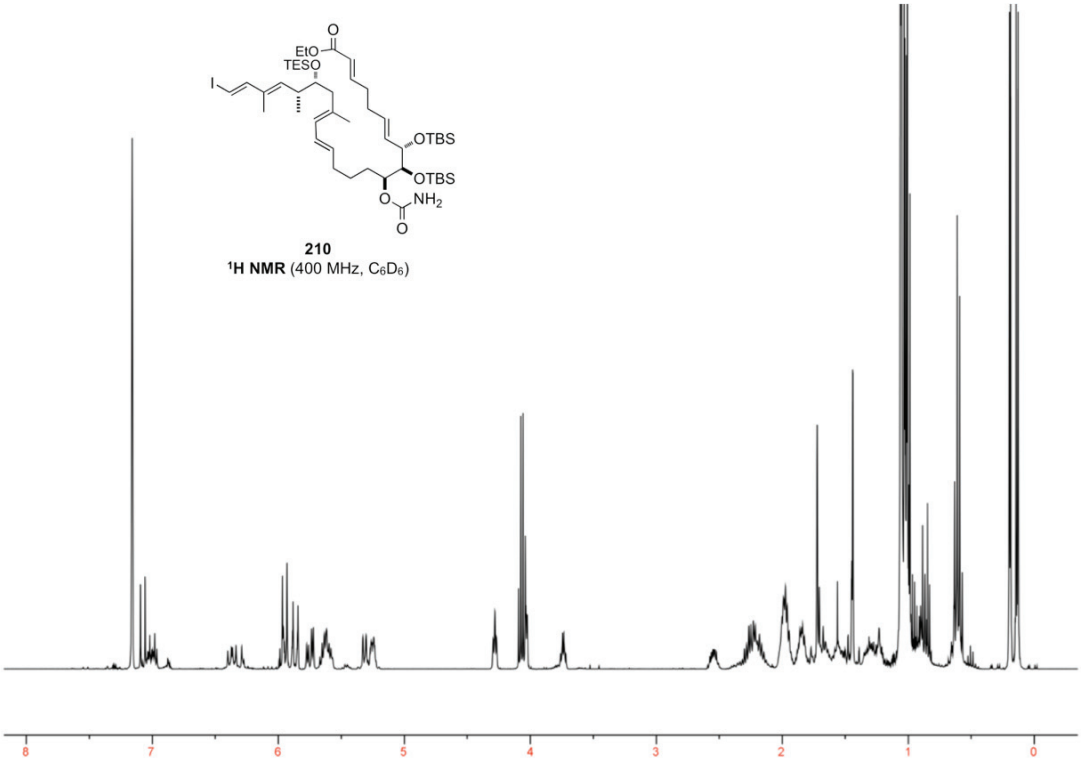
196
^{13}C NMR (100 MHz, C_6D_6)



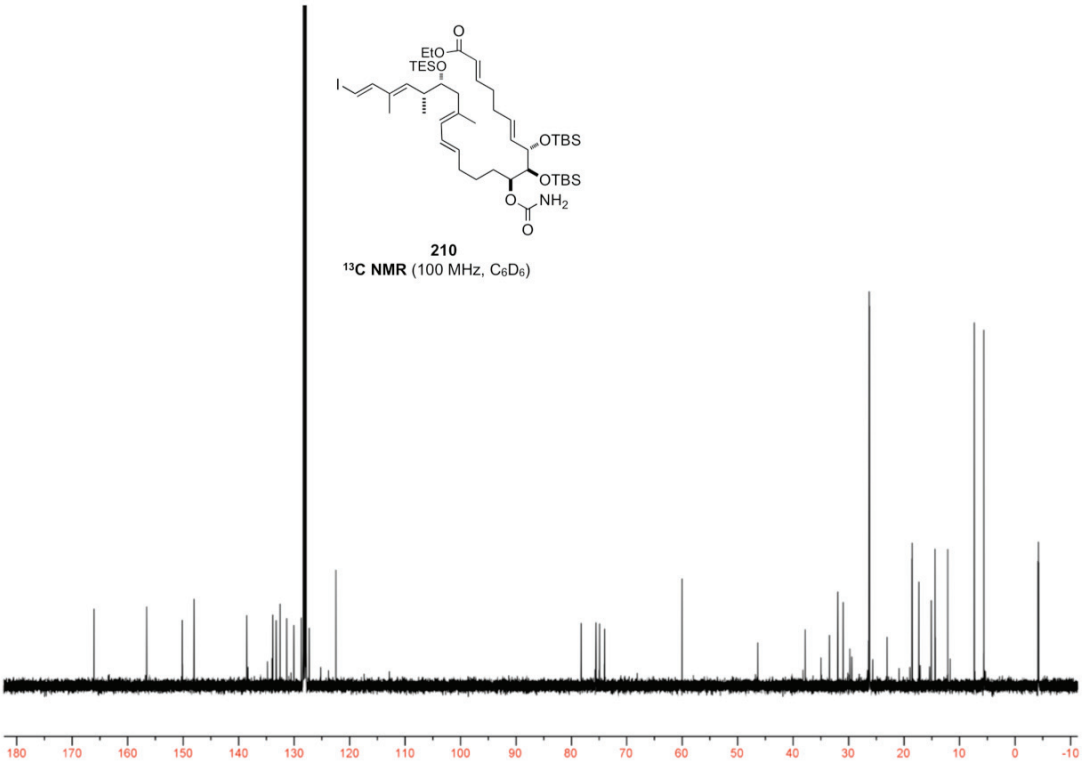
171
^{1}H NMR (400 MHz, C_6D_6)



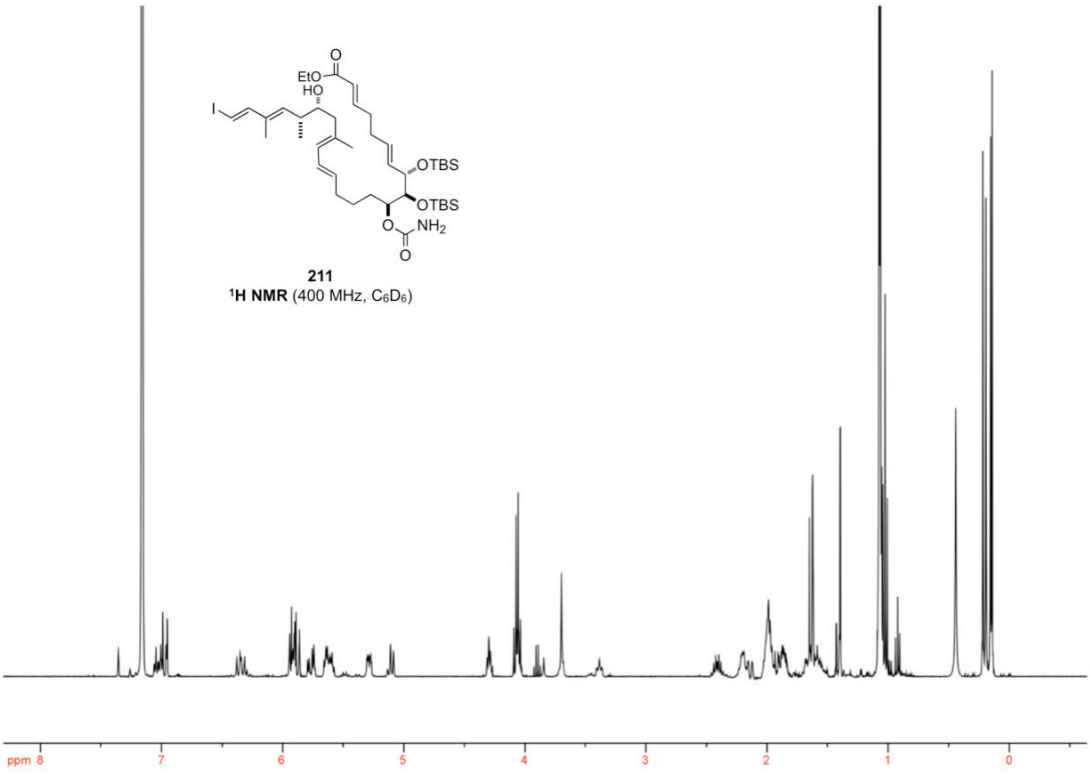
171
^{13}C NMR (100 MHz, C_6D_6)



210
^{1}H NMR (400 MHz, C_6D_6)



210
^{13}C NMR (100 MHz, C_6D_6)



211
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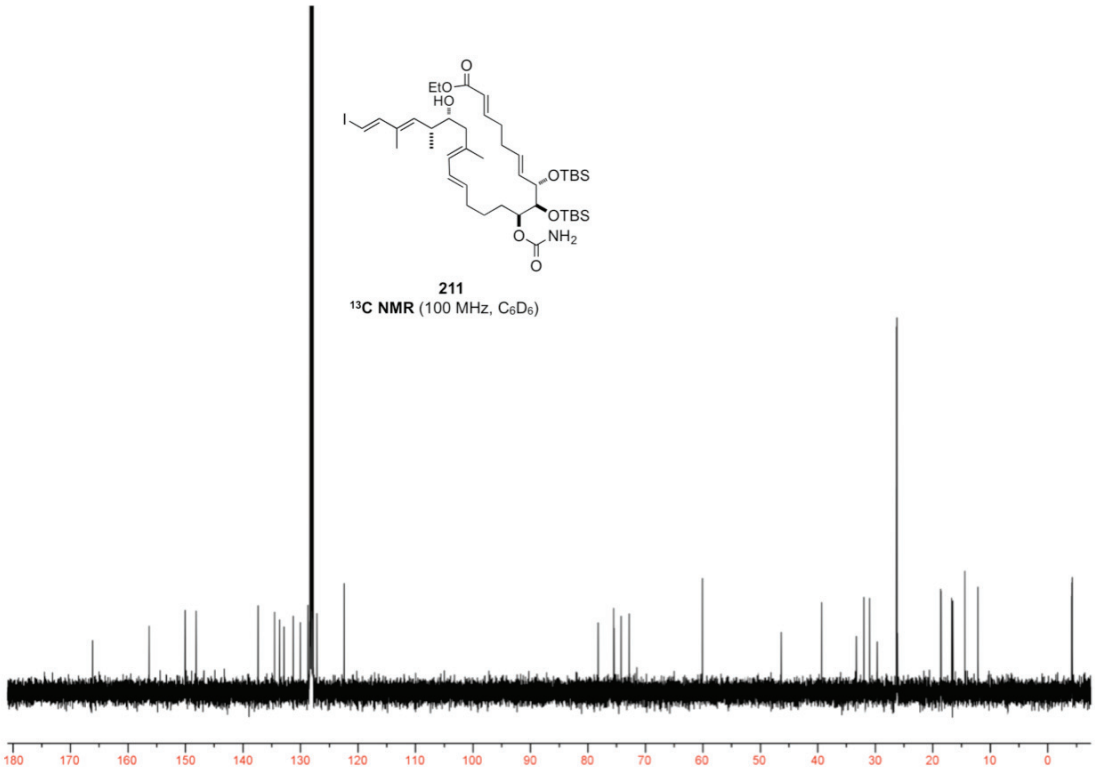
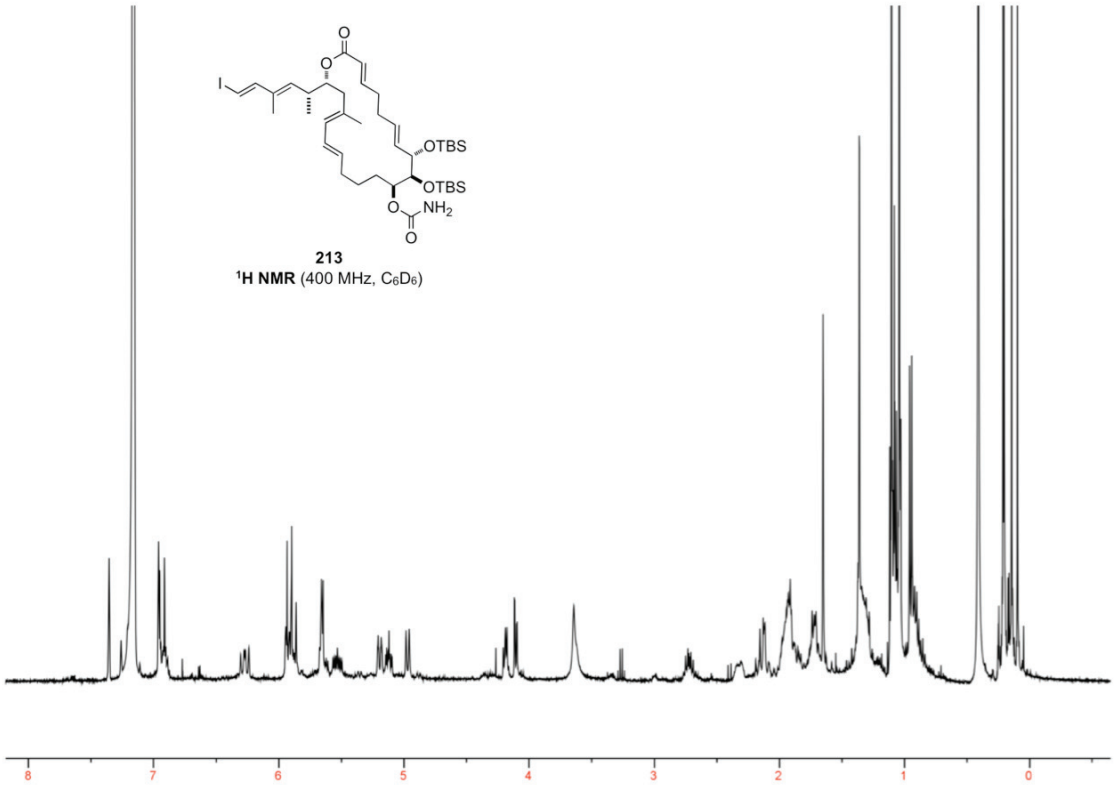
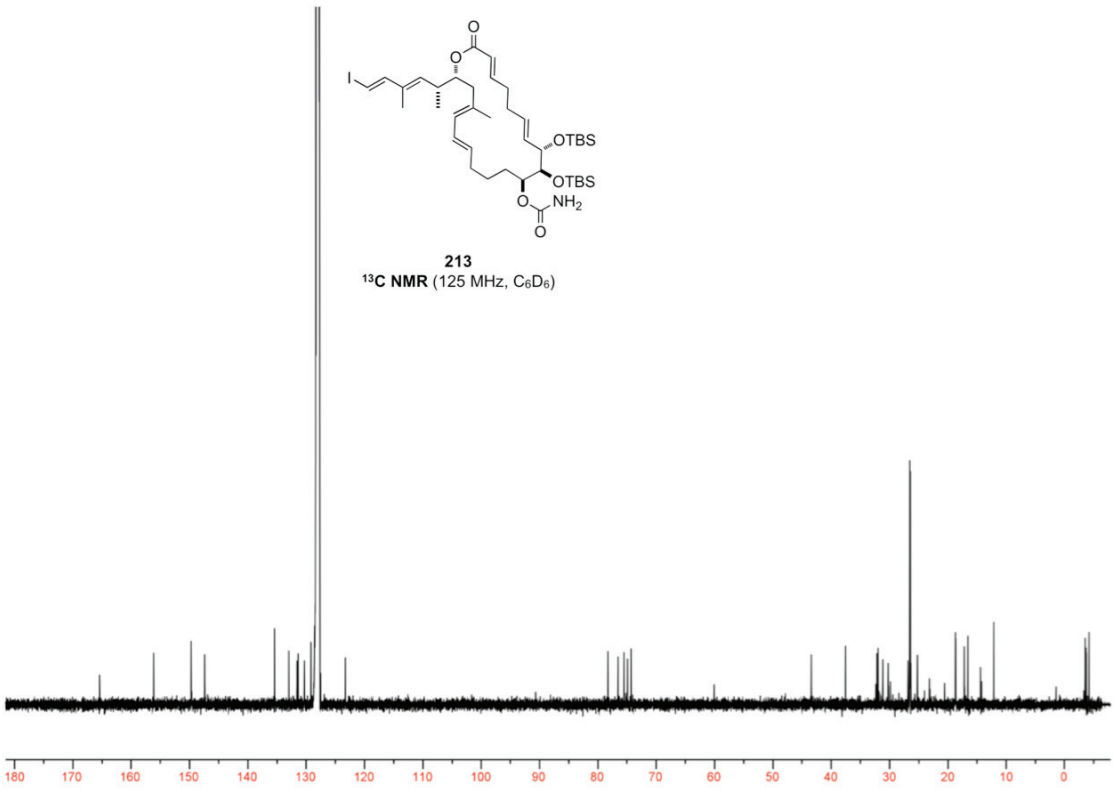
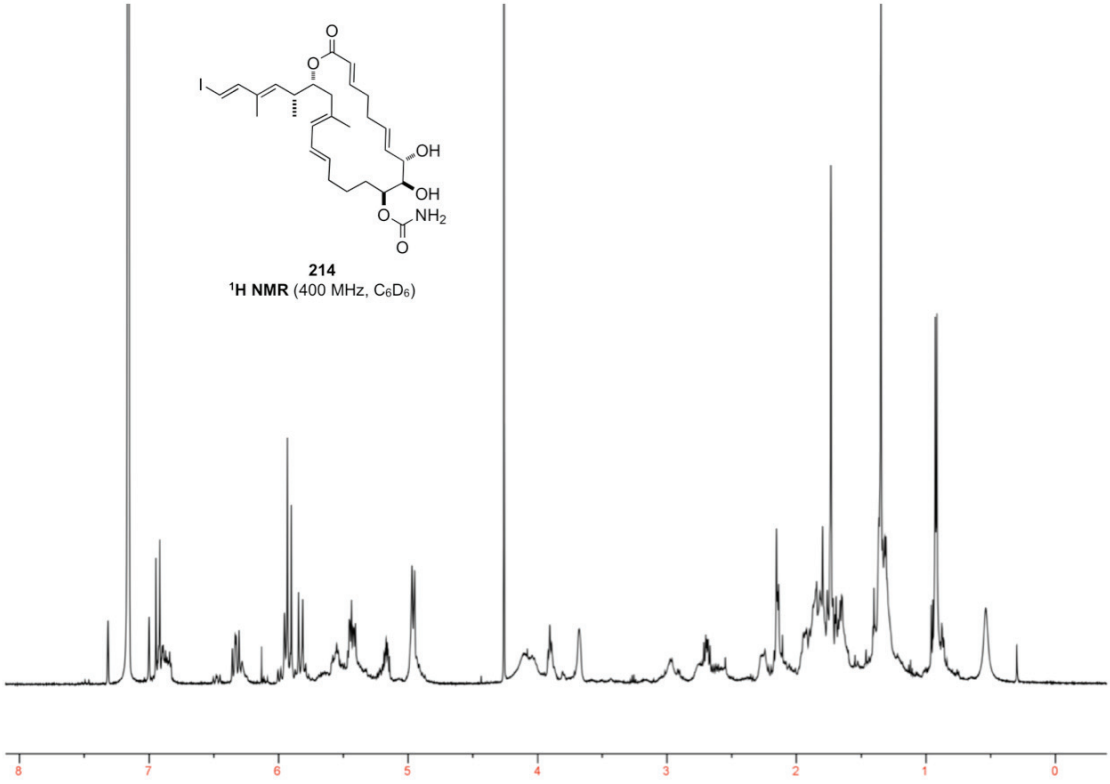


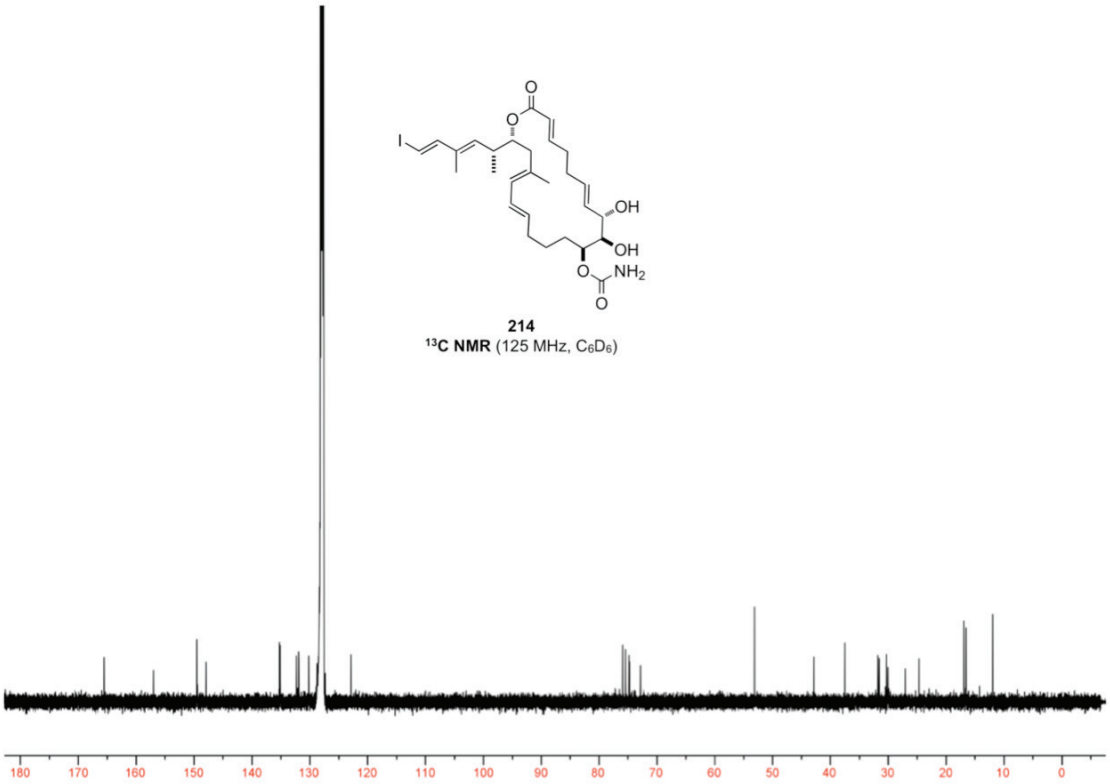
211
^{13}C NMR (100 MHz, C_6D_6)


OTBS
OTBS
NH2
213
1H NMR (400 MHz, C6D6)
8
7
6
5
4
3
2
1
0


OTBS
OTBS
NH2
213
13C NMR (125 MHz, C6D6)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

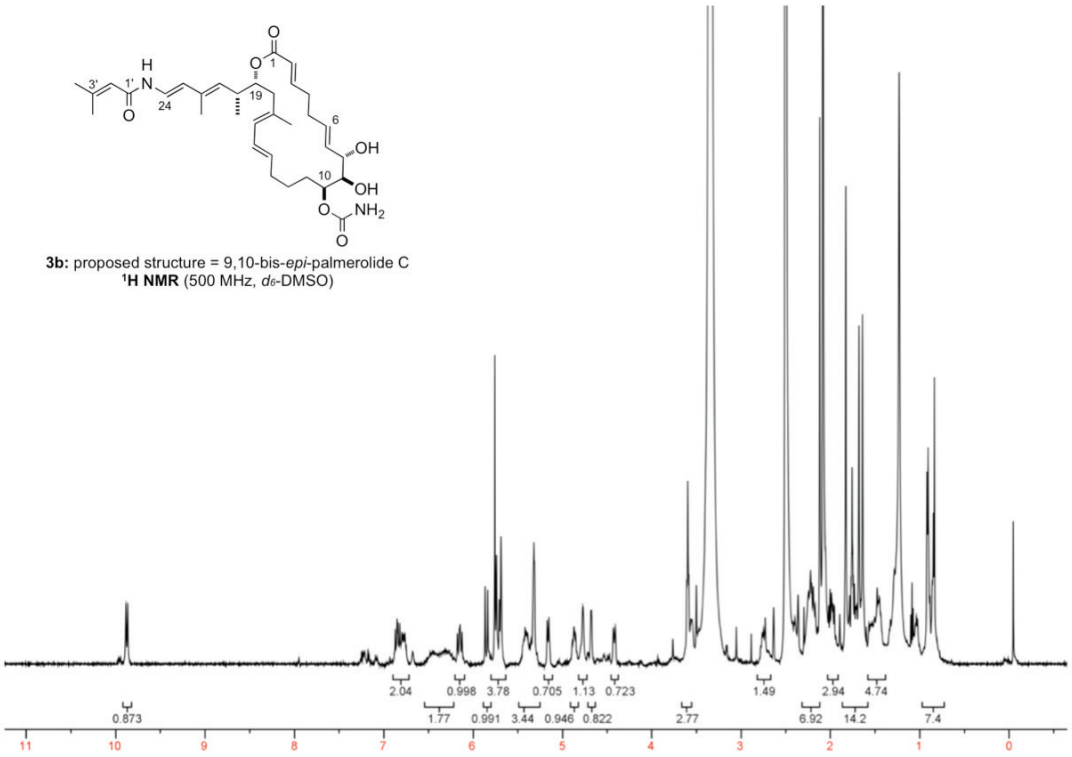


214
^{1}H NMR (400 MHz, C_6D_6)

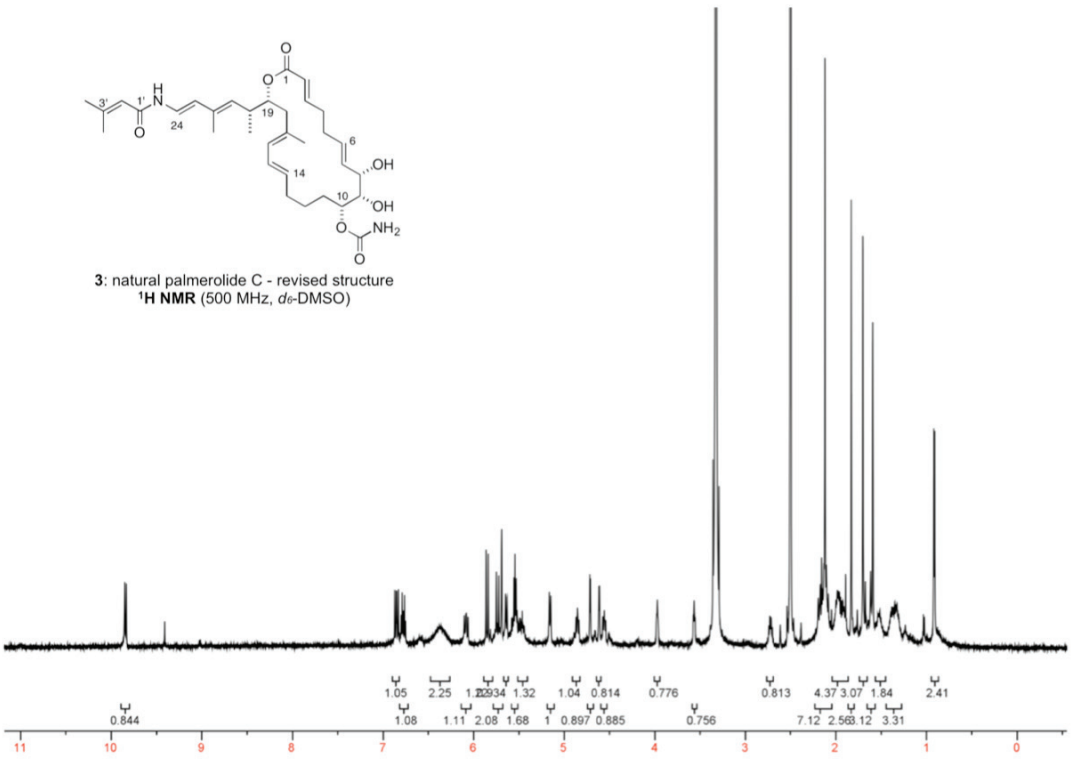


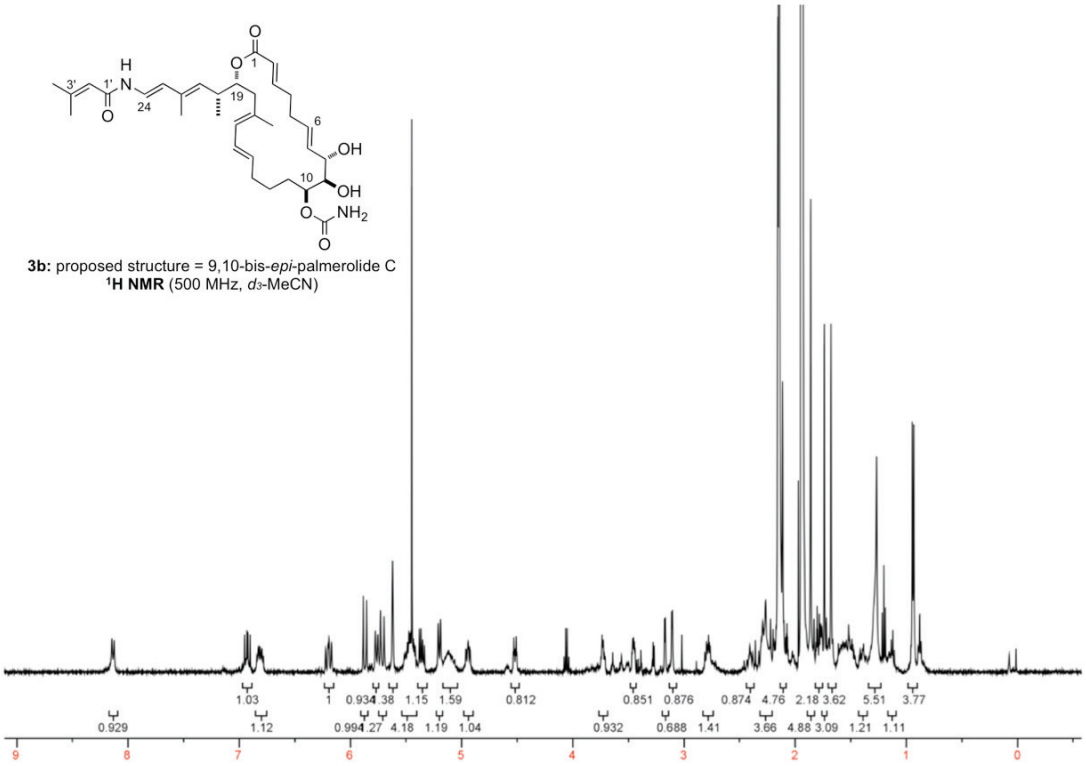
214
^{13}C NMR (125 MHz, C_6D_6)

3b: proposed structure = 9,10-bis-*epi*-palmerolide C
^{1}H NMR (500 MHz, d_6-DMSO)

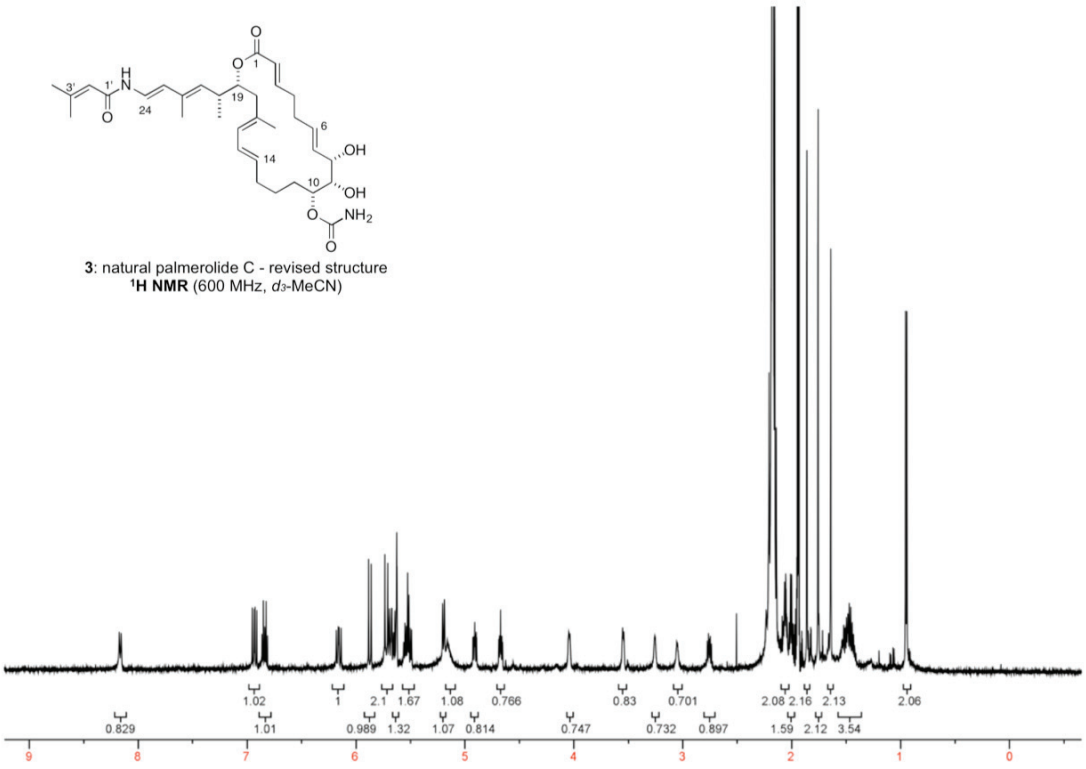


3: natural palmerolide C - revised structure
^{1}H NMR (500 MHz, d_6-DMSO)

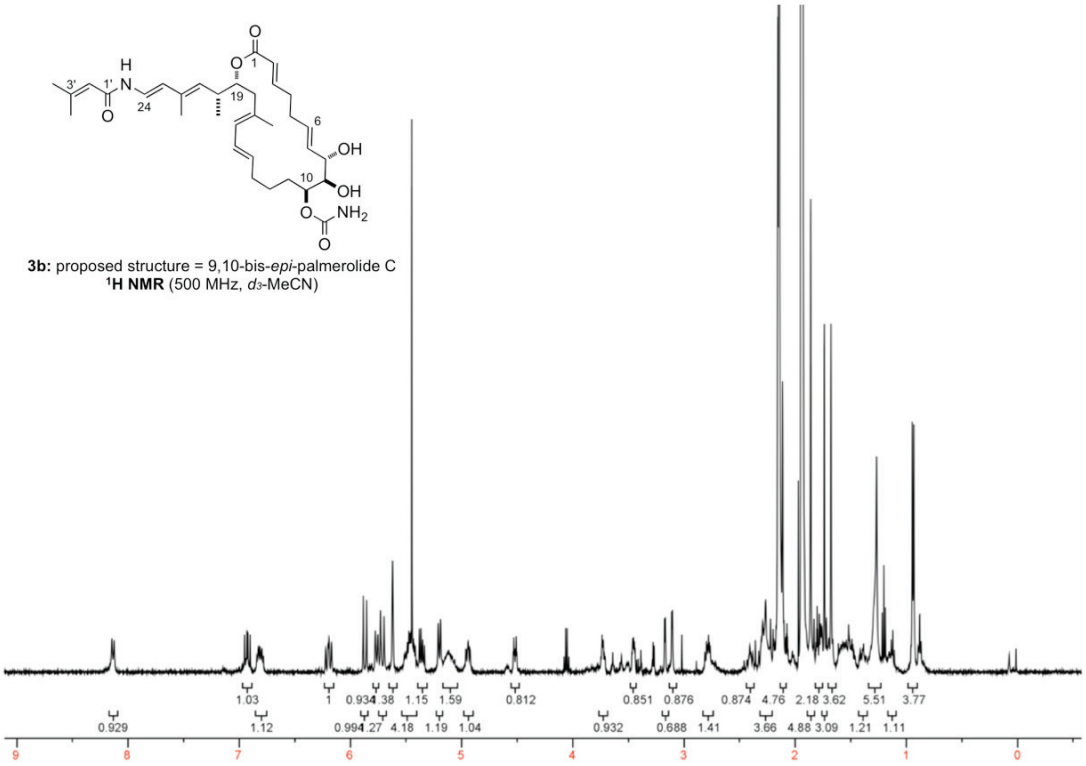




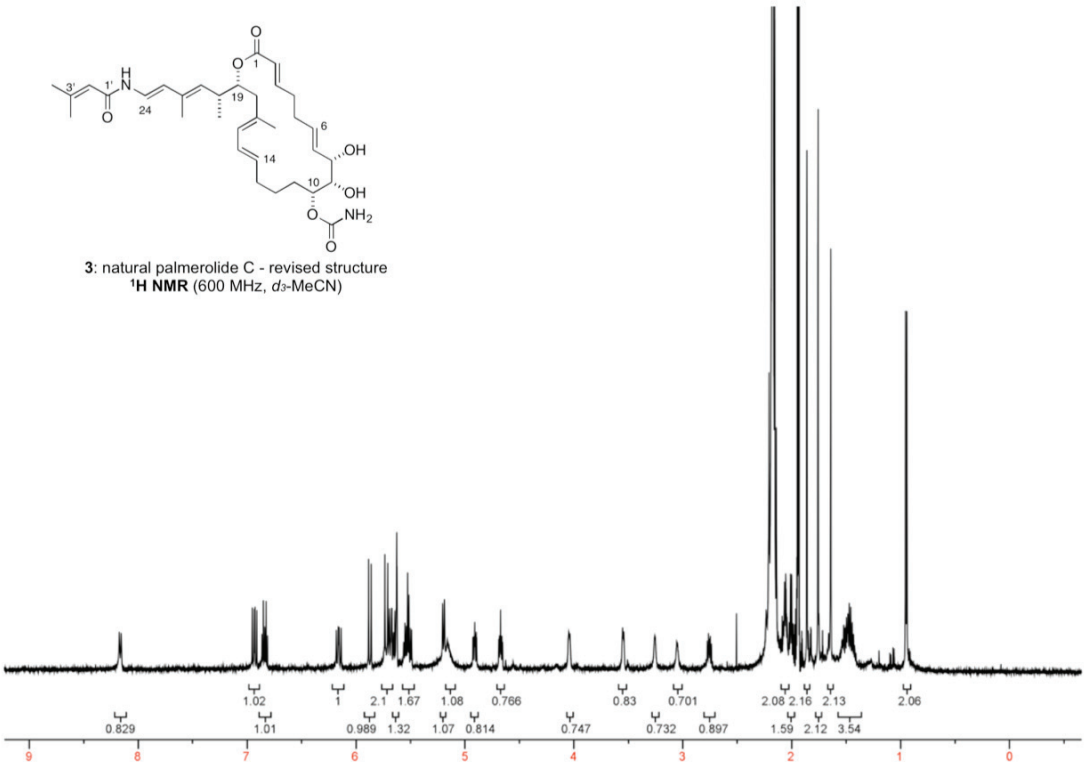
3b: proposed structure = 9,10-bis-*epi*-palmerolide C
^{1}H NMR (500 MHz, d_3-MeCN)



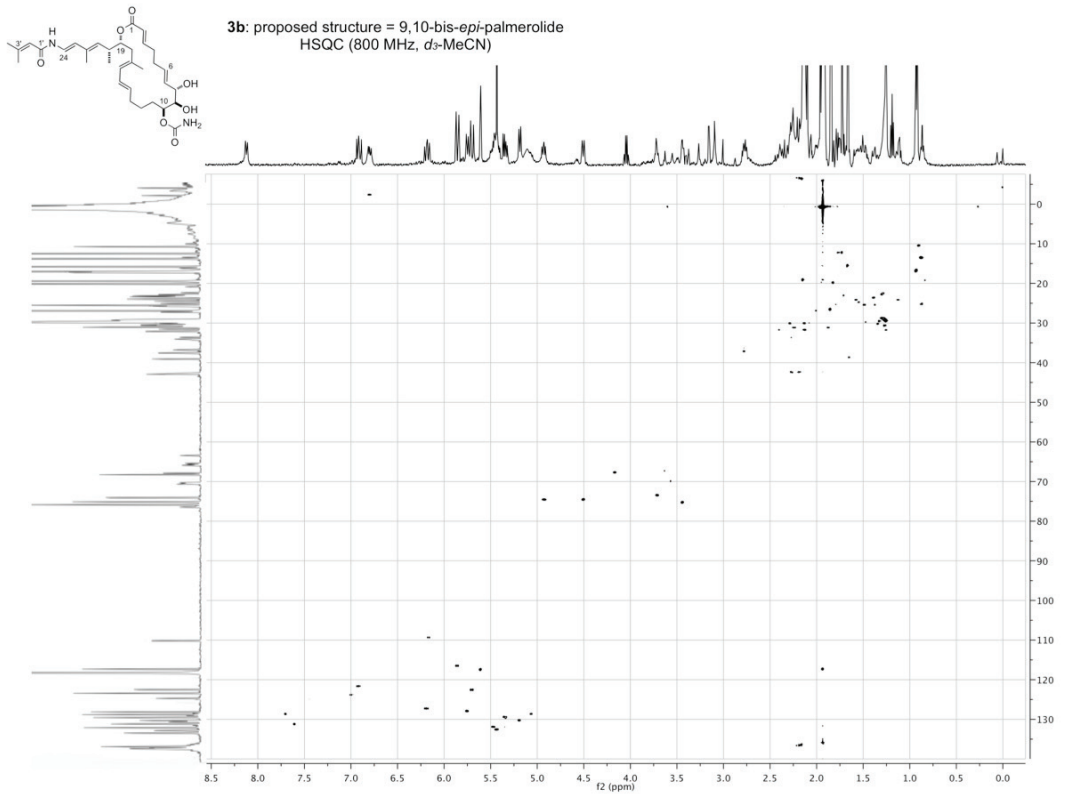
3: natural palmerolide C - revised structure
^{1}H NMR (600 MHz, d_3-MeCN)

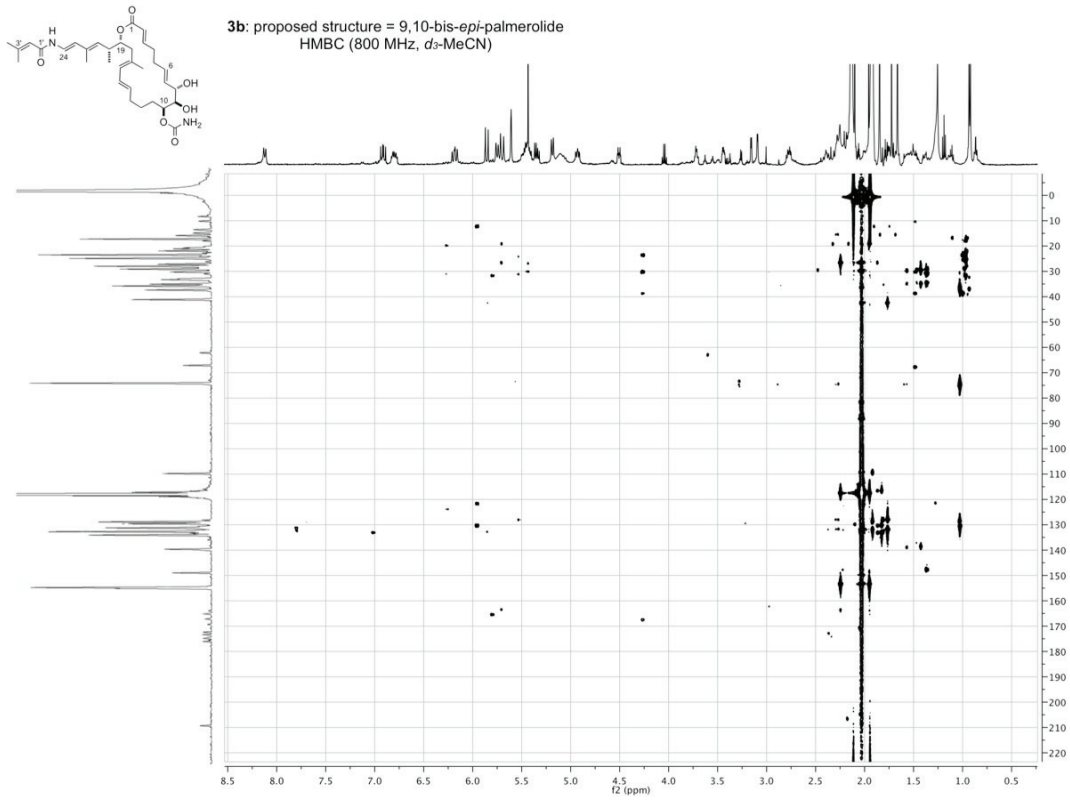


3b: proposed structure = 9,10-bis-*epi*-palmerolide C
^{1}H NMR (500 MHz, d_3-MeCN)



3: natural palmerolide C - revised structure
^{1}H NMR (600 MHz, d_3-MeCN)


3b: proposed structure = 9,10-bis-epi-palmerolide
HSQC (800 MHz, d3-MeCN)
f2 (ppm)


3b: proposed structure = 9,10-bis-epi-palmerolide
HMBC (800 MHz, d3-MeCN)
f2 (ppm)

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